EXHIBIT A

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

MICROSPHERIX LLC, Plaintiff, *v.* MERCK SHARP & DOHME CORP., MERCK SHARP & DOHME B.V., ORGANON USA, INC. AND ORGANON USA, LLC Defendants.	Civil Action No. 2:17-cv-03984 (CCC)(MF)

SECOND AMENDED COMPLAINT FOR PATENT INFRINGEMENT AND DEMAND FOR A JURY TRIAL

Plaintiff Microspherix LLC ("Microspherix"), for its Complaint against Defendants Merck Sharp & Dohme Corp., Merck Sharp & Dohme B.V., Organon USA, Inc. and Organon USA, LLC (collectively, "Merck" or "Defendants"), hereby alleges as follows:

PARTIES

1. Plaintiff Microspherix is a Florida corporation having a principal place of business at 21283 Rockledge Lane, Boca Raton, Florida 33428 in Palm Beach County.

2. Defendant Merck Sharp & Dohme Corp. is a corporation organized and existing under the laws of the State of New Jersey, having a principal place of business at One Merck Drive, Whitehouse Station, New Jersey 08889-0100.

3. Defendant Merck Sharp & Dohme B.V. is incorporated in the Netherlands with a place of business at Waarderweg 39, 2031 BN Haarlem, Netherlands.

4. Defendant Organon USA, Inc. is and/or was a corporation organized and existing under the laws of the State of New Jersey, having a principal place of business at 2000 Galloping Hill Road, Kenilworth, New Jersey, 07033 and One Merck Drive, Whitehouse Station, New Jersey 08889-0100.

5. Defendant Organon USA, LLC is a corporation organized and existing under the laws of the State of New Jersey, having a principal place of business at 2000 Galloping Hill Road, Kenilworth, New Jersey, 07033.

6. Defendant Merck Sharp & Dohme Corp. is and was, at all relevant times, engaged in the business of researching, developing, designing, manufacturing, distributing, supplying, selling, marketing and/or introducing in interstate commerce, either directly or indirectly through third parties or related entities, its products, including the etonogestrel implant, Nexplanon.

7. Nexplanon is manufactured for Defendant Merck Sharp & Dohme Corp.

8. Defendant Merck Sharp & Dohme Corp. conducts and transacts business operations throughout the United States, including in the State of New Jersey, and derives substantial revenue from interstate commerce.

9. United States Patent No. 8,722,037 (the "'037 Patent") is listed in the Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, and identified at

www.merck/com/product/patent/home.html as the patent associated with Defendants' Nexplanon product.

10. The '037 Patent is assigned on the face of the patent to Defendant Merck Sharp & Dohme B.V.

11. Defendant Merck Sharp & Dohme B.V. is and was, at all relevant times, engaged in the business of researching, developing, designing, manufacturing, distributing, supplying, selling, marketing and/or introducing in interstate commerce, either directly or indirectly through third parties or related entities, its products, including the etonogestrel implant, Nexplanon.

12. Defendant Merck Sharp & Dohme B.V. conducts and transacts business operations throughout the United States, including in the State of New Jersey, and derives substantial revenue from interstate commerce.

13. Defendant Organon USA, Inc. was listed as the "Labeler Name" for Nexplanon in the National Drug Code Directory. On information and belief, Defendant Organon USA, LLC is presently listed as the "Labeler Name" for Nexplanon in the National Drug Code Directory.

14. On information and belief, Defendant Organon USA, Inc. was merged into Defendant Organon USA, LLC on or around October 15, 2020 and Defendant Organon USA, LLC is the entity surviving the merger. *See* D.I. 142. Thus, on information and belief, Defendant Organon USA, LLC has assumed the debts and liabilities of Defendant Organon USA, Inc. that have or may result from this Action.

15. A true and correct copy of the National Drug Code Directory for Nexplanon showing Defendant Organon USA, Inc. as the "Labeler Name" as of June 8, 2017 is attached hereto as **Exhibit A**.

16. A true and correct copy of a letter from the FDA to Defendant Organon USA, Inc. regarding the labeling of Nexplanon is attached hereto as **Exhibit B**.

17. According to the FDA website, https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory, a labeler "may be a manufacturer, including a repackager or relabeler, or the entity named on the product label."

18. Defendants Organon USA, Inc. and Organon USA, LLC, are and were, at all relevant times, engaged in the business of researching, developing, designing, manufacturing, distributing, supplying, selling, marketing and/or introducing in interstate commerce, either directly or indirectly through third parties or related entities, its products, including the etonogestrel implant, Nexplanon.

19. Defendants Organon USA, Inc. and Organon USA, LLC conduct and transact business operations throughout the United States, including in the State of New Jersey, and derives substantial revenue from interstate commerce.

NATURE OF THE ACTION

20. This is a claim for patent infringement arising under the Patent Laws of the United States, 35 U.S.C. §§ 100 *et seq*. This action arises out of Defendants' current manufacture, use, sale and/or offer to sell within the United States, Defendants' implantable contraceptive as well as accompanying prescriber and patient information instructing use of this contraceptive.

21. Dr. Edward J. Kaplan is a practicing radiation oncologist and a named inventor on a number of patents directed to medical implant devices which release a therapeutic agent. A distinguishing feature of Dr. Kaplan's claimed inventions relates to a novel and innovative use of

a radiopaque marker to help a physician implant the medical device in the correct location for delivery of a therapeutic agent.

22. Defendants' contraceptive is known as Nexplanon, an etonogestrel implant with a radiopaque marker. Nexplanon was preceded by another implantable contraceptive device known as Implanon, approved in 2001. Implanon lacked a radiopaque marker.

23. Implanon had a propensity to migrate after insertion into the body and become lost. Improper insertion or non-insertion also resulted in unwanted pregnancies. This resulted at least in part from a lack of a means to locate and confirm the correct location of the Implanon device after insertion.

24. Marketing for Implanon in the U.S. ceased by 2012, at which point Nexplanon was the only available single-rod implant in the U.S.

25. Nexplanon improved upon Implanon by including a radiopaque marker allowing for the correct insertion of the device. Nexplanon was also more easily removed than Implanon because it could be located using diagnostic imaging.

JURISDICTION

26. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

27. This Court has personal jurisdiction over Defendant Merck Sharp & Dohme Corp. because, among other reasons, Defendant Merck Sharp & Dohme Corp. is incorporated in the State of New Jersey and has a principal place of business at One Merck Drive, Whitehouse Station, New Jersey 08889-0100.

28. This Court has personal jurisdiction over Defendant Merck Sharp & Dohme Corp. because, among other reasons, Defendant Merck Sharp & Dohme Corp. is registered with the

State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey and having a registered agent for service of process in New Jersey.

29. This Court has personal jurisdiction over Defendant Merck Sharp & Dohme Corp. because, among other reasons, Defendant Merck Sharp & Dohme Corp. has "engaged in substantial and not isolated activity within this state" by conducting and transacting business operations throughout the United States, including in the State of New Jersey, and deriving substantial revenue from interstate commerce.

30. This Court also has personal jurisdiction over Defendant Merck Sharp & Dohme Corp. because, among other reasons, Merck Sharp & Dohme Corp. has established minimum contacts within the forum such that the exercise of jurisdiction over Defendant Merck Sharp & Dohme Corp. will not offend traditional notions of fair play and substantial justice. For instance, Defendant Merck Sharp & Dohme Corp. has placed products that practice the claimed inventions of the Patents-in-Suit into the stream of commerce with the reasonable expectation and/or knowledge that purchasers and users of such products were located within the District of New Jersey. Defendant Merck Sharp & Dohme Corp. has sold, advertised, marketed and/or distributed products in this District that practice the claimed inventions of the Patents-in-Suit.

31. Additionally, this Court also has personal jurisdiction over Defendant Merck Sharp & Dohme Corp. because Merck Sharp & Dohme Corp. has previously elected to avail itself of the benefits of litigating its patent disputes in the District of New Jersey. *See, e.g., Merck Sharp & Dohme Corp. v. Actavis Lab. FL, Inc.*, Civil Action No. 2:15-CV-06541 (D.N.J.); *Merck Sharp & Dohme Corp. v. Impax Labs., Inc.*, Civil Action No. 2:10-CV-04270 (D.N.J.); *Merck Sharp & Dohme Corp. v. Accord Healthcare, Inc.*, Civil Action No. 3:12-CV-03324

(D.N.J.); *Merck Sharp & Dohme Corp. v. Sandoz Inc.,* Civil Action No. 2:12-CV-06077 (D.N.J.).

32. This Court has personal jurisdiction over Defendant Merck Sharp & Dohme B.V. because, among other reasons, Defendant Merck Sharp & Dohme B.V. has "engaged in substantial and not isolated activity within this state" by conducting and transacting business operations throughout the United States, including in the State of New Jersey, and deriving substantial revenue from interstate commerce.

33. This Court also has personal jurisdiction over Defendant Merck Sharp & Dohme B.V. because, among other reasons, Merck Sharp & Dohme B.V. has established minimum contacts within the forum such that the exercise of jurisdiction over Defendant Merck Sharp & Dohme B.V. will not offend traditional notions of fair play and substantial justice. For instance, Defendant Merck Sharp & Dohme B.V. has placed products that practice the claimed inventions of the Patents-in-Suit into the stream of commerce with the reasonable expectation and/or knowledge that purchasers and users of such products were located within the District of New Jersey. Defendant Merck Sharp & Dohme B.V. has manufactured, sold, advertised, marketed and/or distributed products in this District that practice the claimed inventions of the Patents-in-Suit.

34. This Court has personal jurisdiction over Defendant Organon USA, Inc. because, among other reasons, Defendant Organon USA, Inc. is and/or was incorporated in the State of New Jersey and has a principal place of business at 2000 Galloping Hill Road, Kenilworth, New Jersey, 07033 and One Merck Drive, Whitehouse Station, New Jersey 08889-0100.

35. This Court has personal jurisdiction over Defendant Organon USA, Inc. because, among other reasons, Defendant Organon USA, Inc. is and/or was registered with the State of

New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey and having a registered agent for service of process in New Jersey.

36. This Court has personal jurisdiction over Defendant Organon USA, Inc. because, among other reasons, Defendant Organon USA, Inc. has "engaged in substantial and not isolated activity within this state" by conducting and transacting business operations throughout the United States, including in the State of New Jersey, and deriving substantial revenue from interstate commerce.

37. This Court also has personal jurisdiction over Defendant Organon USA, Inc. because, among other reasons, Organon USA, Inc. has established minimum contacts within the forum such that the exercise of jurisdiction over Defendant Organon USA, Inc. will not offend traditional notions of fair play and substantial justice. For instance, Defendant Organon USA, Inc. has placed products that practice the claimed inventions of the Patents-in-Suit into the stream of commerce with the reasonable expectation and/or knowledge that purchasers and users of such products were located within the District of New Jersey. Defendant Organon USA, Inc. has sold, advertised, marketed and/or distributed products in this District that practice the claimed inventions of the Patents-in-Suit.

38. Additionally, this Court also has personal jurisdiction over Defendant Organon USA, Inc. because Organon USA, Inc. has previously elected to avail itself of the benefits of litigating its patent disputes in the District of New Jersey. *See, e.g.*, *Merck & Co., Inc. v. Sun Pharma. Indus., Ltd.*, Civil Action No. 3:12-CV-05374 (D.N.J.).

39. This Court has personal jurisdiction over Defendant Organon USA, LLC because, among other reasons, Defendant Organon USA, LLC is incorporated in the State of New Jersey

and has a principal place of business at 2000 Galloping Hill Road, Kenilworth, New Jersey, 07033.

40. This Court has personal jurisdiction over Defendant Organon USA, LLC because, among other reasons, Defendant Organon USA, LLC is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey and having a registered agent for service of process in New Jersey.

41. This Court has personal jurisdiction over Defendant Organon USA, LLC because, on information and belief and among other reasons, Defendant Organon USA, LLC has "engaged in substantial and not isolated activity within this state" by conducting and transacting business operations throughout the United States, including in the State of New Jersey, and deriving substantial revenue from interstate commerce.

42. This Court also has personal jurisdiction over Defendant Organon USA, LLC because, on information and belief and among other reasons, Organon USA, LLC has established minimum contacts within the forum such that the exercise of jurisdiction over Defendant Organon USA, LLC will not offend traditional notions of fair play and substantial justice. For instance, on information and belief, Defendant Organon USA, LLC has placed products that practice the claimed inventions of the Patents-in-Suit into the stream of commerce with the reasonable expectation and/or knowledge that purchasers and users of such products were located within the District of New Jersey. On information and belief, Defendant Organon USA, LLC has sold, advertised, marketed and/or distributed products in this District that practice the claimed inventions of the Patents-in-Suit.

43. This Court also has personal jurisdiction over Defendant Organon USA, LLC because, among other reasons, this Court has personal jurisdiction over Defendant Organon

USA, Inc., which, on information and belief was fully merged into Defendant Organon USA, LLC on or around October 15, 2020. *See* D.I. 142.

VENUE

44. Venue is proper as to each Defendant in this district pursuant to the provisions of 28 U.S.C. §§ 1391(b)(1), (2), (3) or (c)(3) and 1400.

45. Defendant Merck Sharp & Dohme Corp. is incorporated in the State of New Jersey, has a regular and established place of business at One Merck Drive, Whitehouse Station, New Jersey 08889-0100, and has committed acts of infringement in the District of New Jersey. Accordingly, venue is proper in this district as to Defendant Merck Sharp & Dohme Corp., pursuant to the provisions of 28 U.S.C. § 1400(b).

46. Defendant Organon USA, Inc. is and/or was incorporated in the State of New Jersey, has and/or had a regular and established place of business at 2000 Galloping Hill Road, Kenilworth, NJ, 07033, and One Merck Drive, Whitehouse Station, New Jersey 08889-0100, and has committed acts of infringement in the District of New Jersey. Accordingly, venue is proper in this district as to Defendant Organon USA, Inc., pursuant to the provisions of 28 U.S.C. § 1400(b).

47. Defendant Organon USA, LLC is incorporated in the State of New Jersey, has a regular and established place of business at 2000 Galloping Hill Road, Kenilworth, New Jersey, 07033, has, on information and belief, committed acts of infringement in the District of New Jersey, and is liable for acts of infringement in the District of New Jersey committed by Defendant Organon USA, Inc. Accordingly, venue is proper in this district as to Defendant Organon USA, LLC, pursuant to the provisions of 28 U.S.C. § 1400(b).

48. Defendant Merck Sharp & Dohme B.V. does not reside in the United States. Accordingly, venue is proper in this district pursuant to the provisions of 28 U.S.C. §§ 1391(c)(3) and 1400(b).

THE PATENTS-IN-SUIT

The '402 Patent

49. United States Patent No. 9,636,402 (the "'402 Patent"), titled "Flexible and/or Elastic Brachytherapy Seed or Strand," was duly and legally issued by the United States Patent and Trademark Office on May 2, 2017.

50. A true and correct copy of the '402 Patent is attached hereto as **Exhibit C**.

51. Microspherix is the assignee of the '402 Patent and has the right to sue and recover damages for any current or past infringement of the '402 Patent. The '402 Patent is directed to, among other things, "[a] flexible or elastic brachytherapy strand that includes an imaging marker and/or a therapeutic, diagnostic or prophylactic agent such as a drug in a biocompatible carrier that can be delivered to a subject upon implantation into the subject through the bore of a brachytherapy implantation needle…." ('402 Patent Abstract.)

The '401 Patent

52. United States Patent No. 9,636,401 (the "'401 Patent"), titled "Flexible and/or Elastic Brachytherapy Seed or Strand," was duly and legally issued by the United States Patent and Trademark Office on May 2, 2017.

53. A true and correct copy of the '401 Patent is attached hereto as **Exhibit D**.

54. Microspherix is the assignee of the '401 Patent and has the right to sue and recover damages for any current or past infringement of the '401 Patent.

55. The '401 Patent is directed to, among other things, "[a] flexible or elastic brachytherapy strand that includes an imaging marker and/or a therapeutic, diagnostic or

prophylactic agent such as a drug in a biocompatible carrier that can be delivered to a subject upon implantation into the subject through the bore of a brachytherapy implantation needle…." ('401 Patent Abstract.)

The '835 Patent

56. United States Patent No. 8,821,835 (the "'835 Patent"), titled "Flexible and/or Elastic Brachytherapy Seed or Strand," was duly and legally issued by the United States Patent and Trademark Office on September 2, 2014.

57. A true and correct copy of the '835 Patent is attached hereto as **Exhibit E**.

58. Microspherix is the assignee of the '835 Patent and has the right to sue and recover damages for any current or past infringement of the '835 Patent.

59. The '835 Patent is directed to, among other things, "[a] flexible or elastic brachytherapy strand that includes an imaging marker and/or a therapeutic, diagnostic or prophylactic agent such as a drug in a biocompatible carrier that can be delivered to a subject upon implantation into the subject through the bore of a brachytherapy implantation needle…." ('835 Patent Abstract.)

DEFENDANTS' NEXPLANON PRODUCT

60. Merck developed Nexplanon (etonogestrel implant).

61. Nexplanon consists of an implantable progestin (etonogestrel) contraceptive having a radiopaque, non-radioactive marker, which is pre-loaded in the needle of a disposable applicator.

62. Merck has been advertising, marketing, distributing and/or selling Nexplanon in the United States as of, or subsequent to, 2011.

63. Nexplanon is a follow-on product that replaced a prior medical device known as Implanon.

64. Implanon was advertised, marketed, distributed and/or sold by Merck in the United States as of, or prior to, 2012.

65. Implanon was withdrawn from the United States market at least due in part because of incidences of unwanted pregnancies occurring from improper implantation of the device.

66. A difference between Implanon and Nexplanon is that Nexplanon includes a radiopaque marker.

67. The radiopaque marker allows medical imaging devices such as medical X-ray imaging to be used to assist with locating and situating the implant.

68. Accompanying the Nexplanon product is the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016).

69. A true and correct copy of the Nexplanon Prescribing Information accompanying the Nexplanon product is attached as **Exhibit F**.

70. A true and correct copy of the Nexplanon FDA-Approved Patient Labeling accompanying the Nexplanon product is attached as **Exhibit G**.

71. The Nexplanon Prescribing Information states that Nexplanon has an "Initial U.S. Approval" date of 2001.

COUNT I

Infringement of the '402 Patent

72. The foregoing paragraphs are incorporated by reference as if fully stated herein.

73. In violation of 35 U.S.C. § 271, Defendants are now, and have been directly (literally and/or under the doctrine of equivalents) and/or indirectly (by inducement or contributorily) infringing the '402 Patent.

74. Defendants have had knowledge of infringement of the '402 Patent at least as of the filing of the present complaint, including a letter dated June 5, 2017.

75. Defendants have infringed and continue to infringe one or more claims, including at least Claim 1, of the '402 Patent by making, using, selling, offering for sale, and/or importing Nexplanon.

76. Representative Claim 1 of the '402 Patent recites:

> A strand for administration of a therapeutic agent to a subject in need thereof comprising
>
> (a) a therapeutically effective amount of a therapeutic agent;
>
> (b) a biocompatible component comprising a polymer;
>
> (c) a radio-opaque material, wherein the radio-opaque material is encapsulated in the biocompatible component; and
>
> (d) a polymeric coating,
>
> wherein the therapeutic agent is a small molecule,
>
> wherein the polymeric coating covers the strand and
>
> wherein radiopaque material allows for the position of the strand to be determined following administration[;]
>
> wherein the strand is non-radioactive and does not contain a radioisotope.

('402 Patent at 24:9–19.)

77. Claim 1 of the '402 Patent recites in part, "[a] strand for administration of a therapeutic agent to a subject in need thereof…" ('402 Patent at 24:9–10.) Defendants' Nexplanon product satisfies this claim limitation.

78. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants' Nexplanon product is a "rod shaped implant" which is "4 cm in length with a diameter of 2 mm…." (Nexplanon Prescribing Information at 1, 19.)

79. The ’402 Patent describes a strand, for example, as “typically hav[ing] a size and shape suitable for passing through the bore of a needle having an interior diameter of less than about 2.7 millimeters (10 gauge)….” (’402 Patent at 5:47–50.)

80. The diameter of Nexplanon is 2 millimeters, which is less than 2.7 millimeters.

81. Thus, Defendants’ Nexplanon product can pass through the bore of a needle having an interior diameter of less than 2.7 millimeters.

82. As such, Defendants’ Nexplanon product may be considered, among other things, a strand.

83. Nexplanon contains “a progestin indicated for use by women to prevent pregnancy.” (Nexplanon Prescribing Information at 1.)

84. Accordingly, Defendants’ Nexplanon product (a strand) administers a therapeutic agent to a person in need thereof.

85. Claim 1 of the ’402 Patent also recites in part, “(a) a therapeutically effective amount of a therapeutic agent…” (’402 Patent at 24:10–11.) Defendants’ Nexplanon product satisfies this claim limitation.

86. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants’ Nexplanon product is comprised of “68 mg of the synthetic progestin etonogestrel,” which has been found by the FDA to be safe and effective in preventing pregnancy. (Nexplanon Prescribing Information at 1, 19.)

87. Accordingly, Defendants’ Nexplanon product comprises a therapeutically effective amount of a therapeutic agent.

88. Claim 1 of the ’402 Patent also recites in part, “(b) a biocompatible component comprising a polymer…” (’402 Patent at 24:11–12.) Defendants’ Nexplanon product satisfies this claim limitation.

89. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants’ Nexplanon product is comprised of “an ethylene vinyl acetate (EVA) copolymer core.” (Nexplanon Prescribing Information at 19.)

90. Nexplanon has been approved by the FDA, and Nexplanon is comprised of EVA (a polymer). (Nexplanon Prescribing Information at 1, 19.)

91. EVA has been approved for human use by the FDA.

92. EVA is biocompatible.

93. Accordingly, Defendants’ Nexplanon product is comprised of a biocompatible component comprising a polymer.

94. Claim 1 of the ’402 Patent also recites in part, “a radio-opaque material, wherein the radio-opaque material is encapsulated in the biocompatible component…” (’402 Patent at 24:12–14.) Defendants’ Nexplanon product satisfies this claim limitation.

95. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants’ Nexplanon product is comprised of “an ethylene vinyl acetate (EVA) copolymer core, containing 68 mg of the synthetic progestin etonogestrel, barium sulfate (radiopaque ingredient), and may also contain magnesium stearate….” (Nexplanon Prescribing Information at 19.)

96. Accordingly, the radiopaque material (barium sulfate) is encapsulated in the biocompatible component (EVA copolymer core).

97. Claim 1 of the '402 Patent also recites in part, "(d) a polymeric coating…" ('402 Patent at 24:14.) Defendants' Nexplanon product satisfies this claim limitation.

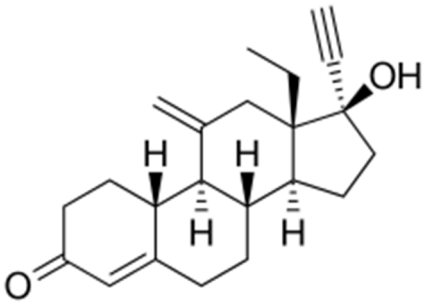
98. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants' Nexplanon product is comprised of an "EVA copolymer core, containing 68 mg of the synthetic progestin etonogestrel, barium sulfate (radiopaque ingredient), and may also contain magnesium stearate, surrounded by an EVA copolymer skin." (Nexplanon Prescribing Information at 19.)

99. Accordingly, the "EVA copolymer skin" is a polymeric coating.

100. Claim 1 of the '402 Patent also recites in part, "wherein the therapeutic agent is a small molecule…" ('402 Patent at 24:15.) Defendants' Nexplanon product satisfies this claim limitation.

101. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants' Nexplanon product is comprised of the active ingredient etonogestrel, also known as 13-Ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one. (Nexplanon Prescribing Information at 19.)

102. Etonogestrel is a chemical compound having a molecular weight of about 324.46 g/mol and the following chemical structure:



(Nexplanon Prescribing Information at 19.)

103. Accordingly, Defendants' Nexplanon product is comprised of a small molecule therapeutic agent.

104. Claim 1 of the '402 Patent also recites in part, "wherein the polymeric coating covers the strand…" ('402 Patent at 24:15–16.) Defendants' Nexplanon product satisfies this claim limitation.

105. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants' Nexplanon product is comprised of an "EVA copolymer core, containing 68 mg of the synthetic progestin etonogestrel, barium sulfate (radiopaque ingredient), and may also contain magnesium stearate, surrounded by an EVA copolymer skin." (Nexplanon Prescribing Information at 19.)

106. Accordingly, the polymeric coating (EVA copolymer skin) surrounds (covers) the strand.

107. Claim 1 of the '402 Patent also recites in part, "wherein radiopaque material allows for the position of the strand to be determined following administration…" ('402 Patent at 24:16–18.) Defendants' Nexplanon product satisfies this claim limitation.

108. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants' Nexplanon product is comprised of barium sulfate, a radiopaque material, which allows for the position of the strand to be determined following administration, for example, by medical X-ray imaging. (Nexplanon Prescribing Information at 7, 19.)

109. Claim 1 of the '402 Patent also recites in part, "wherein the strand is non-radioactive and does not contain a radioisotope…" ('402 Patent at 24:18–19.) Defendants' Nexplanon product satisfies this claim limitation.

110. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), do not indicate that Defendants' Nexplanon product is radioactive, or contains radioisotopes.

111. If Defendants' Nexplanon product contained radioactive materials, the Nexplanon Prescribing Information and/or Nexplanon FDA-Approved Patient Labeling would indicate this.

112. Accordingly, Defendants' Nexplanon product is non-radioactive and does not contain a radioisotope.

113. Defendants directly infringe (literally or under the doctrine of equivalents) and/or indirectly infringe (by inducement or contributorily) the claims of the '402 Patent before the expiration thereof, including but not limited to, representative Claim 1 as well as Claims 2–19.

114. Defendants' Nexplanon product is accompanied by the Nexplanon Prescribing Information, directed primarily to health-care providers, as well as the FDA-Approved Patient Labeling, directed primarily to patients. (*See, e.g.,* **Exhibits F and G**.)

115. The Nexplanon Prescribing Information expressly encourages and instructs healthcare providers to use Defendants' Nexplanon product in their patients.

116. The FDA-Approved Patient Labeling expressly encourages use of Defendants' Nexplanon product by patients under the direction of a healthcare provider.

117. Thus, a patient and/or healthcare provider, following the Nexplanon Prescribing Information and/or FDA-Approved Patient Labeling, will infringe the '402 Patent by using Defendants' Nexplanon product.

118. Defendants know or should reasonably know that distributing the Nexplanon Prescribing Information and FDA-Approved Patient Labeling with Nexplanon will induce

healthcare providers and/or patients to use Defendants' Nexplanon product, or contribute to an infringing use of Defendants' Nexplanon product.

119. Defendants, as well as patients and healthcare providers following the Nexplanon Prescribing Information or FDA-Approved Patient Labeling, directly and/or indirectly infringe literally and/or under the doctrine of equivalents, the '402 Patent.

120. Neither Nexplanon nor the use of Nexplanon according to the Nexplanon Prescribing Information are a staple article or commodity of commerce suitable for substantial noninfringing use.

121. Microspherix has been and continues to be damaged by Defendants infringement of the '402 Patent.

122.

COUNT II

Infringement of the '401 Patent

123. The foregoing paragraphs are incorporated by reference as if fully stated herein.

124. In violation of 35 U.S.C. § 271, Defendants are now, and have been directly (literally or under the doctrine of equivalents) and/or indirectly (by inducement or contributorily) infringing the '401 Patent.

125. Defendants have had knowledge of infringement of the '401 Patent at least as of the filing of the present complaint, including a letter dated June 5, 2017.

126. Defendants have infringed and continue to infringe one or more claims, including at least Claim 1, of the '401 Patent by making, using, selling, offering for sale, and/or importing Nexplanon.

127. Representative Claim 1 of the '401 Patent recites:

A flexible non-radioactive strand for implantation into a subject, comprising:

> a marker component configured to allow for the determination of the position of the strand within a target tissue,
>
> the marker component having a length extending along a centerline of the marker component between a first end and a second end and having a substantially continuous wall bounding a hollow interior;
>
> a biocompatible component; and
>
> a therapeutic, prophylactic, and/or diagnostic agent,
>
> wherein the marker, biocompatible component and agent are disposed within the hollow interior;
>
> wherein the length of the marker component is greater than the diameter of the hollow interior, and
>
> wherein the substantially continuous wall includes at least one opening adapted to allow the agent to pass out of the hollow interior[;]
>
> wherein the strand do not contain a radioisotope.

('401 Patent at 24:2–20.)

128. Claim 1 of the '401 Patent recites in part, "[a] flexible non-radioactive strand for implantation into a subject…" ('401 Patent at 24:2–3.) Defendants' Nexplanon product satisfies this claim limitation.

129. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants' Nexplanon product is a "soft, flexible" "rod shaped implant" which is "4 cm in length with a diameter of 2 mm…." (Nexplanon Prescribing Information at 1, 19.)

130. The '401 Patent describes a strand, for example, as "typically hav[ing] a size and shape suitable for passing through the bore of a needle having an interior diameter of less than about 2.7 millimeters (10 gauge)…" ('401 Patent at 5:42–45.)

131. The diameter of Nexplanon is 2 millimeters, which is less than 2.7 millimeters.

132. Thus, Defendants' Nexplanon product can pass through the bore of a needle having an interior diameter of less than 2.7 millimeters.

133. As such, Defendants' Nexplanon product may be considered, among other things, a strand.

134. The Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), do not indicate that Defendants' Nexplanon product is radioactive.

135. If Defendants' Nexplanon product contained radioactive materials, the Nexplanon Prescribing Information and/or Nexplanon FDA-Approved Patient Labeling would indicate this.

136. Nexplanon is implanted into subjects, e.g., for use as a contraceptive. (Nexplanon Prescribing Information at 1.)

137. Accordingly, Defendants' Nexplanon product is a flexible, non-radioactive strand which is implanted into a subject.

138. Claim 1 of the '401 Patent also recites in part, "a marker component configured to allow for the determination of the position of the strand within a target tissue…" ('401 Patent at 24:4–6.) Defendants' Nexplanon product satisfies this claim limitation.

139. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), the Nexplanon implant is comprised of "an ethylene vinyl acetate (EVA) copolymer core, containing 68 mg of the synthetic progestin etonogestrel, barium sulfate (radiopaque ingredient), and may also contain magnesium stearate, surrounded by an EVA copolymer skin." (Nexplanon Prescribing Information at 19.)

140. Thus, the marker component is comprised of the EVA copolymer core, which contains barium sulfate (a radiopaque ingredient), and the EVA copolymer skin, which surrounds the EVA copolymer core.

141. The Nexplanon Prescribing Information recites the following: "[i]nsert one NEXPLANON subdermally just under the skin at the inner side of the non-dominant upper arm." (Nexplanon Prescribing Information at 1); "[a]lways verify the presence of the implant in the woman's arm immediately after insertion by palpation." (Nexplanon Prescribing Information at 6); "[i]f the rod is not palpable … [u]se other methods to confirm the presence of the implant. Given the radiopaque nature of the implant, suitable methods for localization are two-dimensional X-ray and X-ray computerized tomography (CT scan)" (Nexplanon Prescribing Information at 7).

142. Accordingly, the marker component is configured to allow for the determination of the position of the Nexplanon product (the strand) within a target tissue.

143. Claim 1 of the '401 Patent also recites in part, "the marker component having a length extending along a centerline of the marker component between a first end and a second end and having a substantially continuous wall bounding a hollow interior…" ('401 Patent at 24:6–10.) Defendants' Nexplanon product satisfies this claim limitation.

144. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants' Nexplanon product is "rod shaped" (Nexplanon Prescribing Information at 1.)

145. Defendants' Nexplanon product is comprised of an EVA copolymer core, "surrounded by an EVA copolymer skin." (Nexplanon Prescribing Information at 19.)

146. The EVA copolymer skin and the EVA copolymer core (marker component) is rod-shaped. (Nexplanon Prescribing Information at 1, 19.)

147. The rod-shaped marker component has a length extending along a centerline of the marker component. (Nexplanon Prescribing Information at 1, 19.)

148. The rod-shaped marker component has a first end and a second end. (Nexplanon Prescribing Information at 1, 19.)

149. The ’037 Patent, which discloses Defendants’ Nexplanon product, describes the “[p]reparation of a two layered implant … consisting of the core and a skin layer of EVA-14 copolymer.” (’037 Patent at 5:8–14.)

150. The EVA copolymer skin surrounding the EVA copolymer core forms or is part of a substantially continuous wall.

151. Since the EVA copolymer skin surrounds the EVA copolymer core, the EVA copolymer skin would have an interior (hollow) space.

152. Thus, the marker component, which is comprised of the EVA copolymer skin and EVA copolymer core, has a length extending along a centerline of the marker component between a first end and a second end, and the EVA copolymer skin of the marker component has or forms part of a substantially continuous wall bounding an interior (hollow) space.

153. Claim 1 of the ’401 Patent also recites in part, “a biocompatible component…” (’401 Patent at 24:10.) Defendants’ Nexplanon product satisfies this claim limitation.

154. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants’ Nexplanon product is comprised of “an ethylene vinyl acetate (EVA) copolymer core.” (Nexplanon Prescribing Information at 19.)

155. Nexplanon has been approved by the FDA, and Nexplanon is comprised of EVA. (Nexplanon Prescribing Information at 1, 19.)

156. EVA has been approved for human use by the FDA.

157. EVA is biocompatible.

158. Accordingly, Defendants' Nexplanon product is comprised of a biocompatible component.

159. Claim 1 of the '401 Patent also recites in part, "a therapeutic, prophylactic, and/or diagnostic agent…" ('401 Patent at 24:11.) Defendants' Nexplanon product satisfies this claim limitation.

160. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants' Nexplanon product is comprised of "68 mg of the synthetic progestin etonogestrel," which has been found by the FDA to be safe and effective in preventing pregnancy. (Nexplanon Prescribing Information at 1, 19.)

161. Accordingly, Defendants' Nexplanon product is comprised of a therapeutic and/or prophylactic agent.

162. Claim 1 of the '401 Patent also recites in part, "wherein the marker, biocompatible component and agent are disposed within the hollow interior…" ('401 Patent at 24:12-14.) Defendants' Nexplanon product satisfies this claim limitation.

163. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants' Nexplanon product is comprised of an "EVA copolymer core, containing 68 mg of the synthetic progestin etonogestrel, barium sulfate (radiopaque ingredient), and may also contain magnesium stearate, surrounded by an EVA copolymer skin." (Nexplanon Prescribing Information at 19.)

164. The EVA copolymer core contains a biocompatible component (EVA), a radiopaque marker (barium sulfate), and a therapeutic agent (etonogestrel). (Nexplanon Prescribing Information at 19.)

165. Accordingly, the marker (barium sulfate), biocompatible component (EVA copolymer core) and agent (etonogestrel) are disposed within the interior (hollow) space, bounded at least in part by the EVA copolymer skin of the marker component.

166. Claim 1 of the '401 Patent also recites in part, "wherein the length of the marker component is greater than the diameter of the hollow interior…" ('401 Patent at 24:14–16.) Defendants' Nexplanon product satisfies this claim limitation.

167. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants' Nexplanon product is a "rod shaped implant" which is "4 cm in length with a diameter of 2 mm…." (Nexplanon Prescribing Information at 1, 19.)

168. Accordingly, the length of Defendants' Nexplanon product (4 cm) is greater than the diameter of its interior (no more than 2 mm).

169. Defendants' Nexplanon product is comprised of an EVA copolymer core, "surrounded by an EVA copolymer skin." (Nexplanon Prescribing Information at 19.)

170. The marker component of Nexplanon has an aspect ratio that is the same or substantially the same as the Nexplanon product.

171. For example, Example 1 of the '037 Patent, describes the "preparation of a two layered implant … consisting of the core and a skin layer of EVA-14 copolymer." ('037 Patent at 5:8–14.)

172. Example 1 of the '037 Patent further recites, "[e]xtrusion lead to a co-axial fiber with a diameter of 2 mm and a skin thickness of 60 µm." ('037 Patent at 5:34–35.)

173. Thus, the interior (hollow) space, bounded by the EVA copolymer skin of the marker component, has a diameter of no more than 2 mm.

174. Moreover, the ’037 Patent recites, “[t]he coaxial fiber was cut into 4.0 cm rods using a semiautomatic cutter (Diosynth or equivalent).” (’037 Patent at 5:37–38.)

175. Thus, the length of the marker component, which is comprised of the EVA copolymer skin and the EVA copolymer core, is 4 cm (40 mm).

176. Thus, accounting for the thickness of the EVA copolymer skin, the length of the marker component (40 mm) is greater than the diameter of the interior (hollow) space (no more than 2 mm).

177. Claim 1 of the ’401 Patent also recites in part, “wherein the substantially continuous wall includes at least one opening adapted to allow the agent to pass out of the hollow interior…” (’401 Patent at 24:17–19.) Defendants’ Nexplanon product satisfies this claim limitation.

178. The ’037 Patent, which discloses Defendants’ Nexplanon product recites, “[i]t can therefore be concluded that no or hardly any barium sulphate crystals migrated out of the implant through the open ends.” (’037 Patent at 9:4–6.)

179. The Nexplanon Prescribing Information recites, “[a]fter subdermal insertion of the etonogestrel implant, etonogestrel is released into the circulation and is approximately 100% bioavailable.” (Nexplanon Prescribing Information at 19.)

180. Accordingly, Defendants’ Nexplanon product includes at least one opening in its substantially continuous wall which allows the therapeutic agent to migrate out of the implant.

181. Claim 1 of the ’401 Patent also recites in part, “wherein the strand do[es] not contain a radioisotope…” (’401 Patent at 24:19–20.) Defendants’ Nexplanon product satisfies this claim limitation.

182. The Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), do not indicate that Defendants' Nexplanon product contains radioisotopes.

183. If Defendants' Nexplanon product contained radioisotopes, the Nexplanon Prescribing Information and/or Nexplanon FDA-Approved Patient Labeling would indicate this.

184. Accordingly, Defendants' Nexplanon product does not contain a radioisotope.

185. Defendants directly infringe (literally or under the doctrine of equivalents) and/or indirectly infringe (by inducement or contributorily) the claims of the '401 Patent before the expiration thereof, including but not limited to, representative Claim 1 and Claims 2–5, 13–16, 18–20, 23–25.

186. Defendants' Nexplanon product is accompanied by the Nexplanon Prescribing Information, directed primarily to health-care providers, as well as the FDA-Approved Patient Labeling, directed primarily to patients. (*See, e.g.*, **Exhibits F and G**.)

187. The Nexplanon Prescribing Information expressly encourages and instructs healthcare providers to use Defendants' Nexplanon product in their patients.

188. The FDA-Approved Patient Labeling expressly encourages use of Defendants' Nexplanon product by patients under the direction of a healthcare provider.

189. Thus, a patient and/or healthcare provider, following the Nexplanon Prescribing Information and/or FDA-Approved Patient Labeling, will infringe the '401 Patent by using Defendants' Nexplanon product.

190. Defendants know or should reasonably know that distributing the Nexplanon Prescribing Information and FDA-Approved Patient Labeling with Nexplanon will induce

healthcare providers and/or patients to use Defendants' Nexplanon product, or contribute to an infringing use of Defendants' Nexplanon product.

191. Defendants, as well as patients and healthcare providers following the Nexplanon Prescribing Information or FDA-Approved Patient Labeling, directly and/or indirectly infringe literally and/or under the doctrine of equivalents, the '401 Patent.

192. Neither Nexplanon nor the use of Nexplanon according to the Nexplanon Prescribing Information are a staple article or commodity of commerce suitable for substantial noninfringing use.

193. Microspherix has been and continues to be damaged by Defendants infringement of the '401 Patent.

COUNT III

Infringement of the '835 Patent

194. The foregoing paragraphs are incorporated by reference as if fully stated herein.

195. In violation of 35 U.S.C. § 271, Defendants are now, and have been directly (literally or under the doctrine of equivalents) and/or indirectly (by inducement or contributorily) infringing the '835 Patent.

196. Defendants have had knowledge of infringement of the '835 Patent at least as of the filing of the present complaint, including a letter dated June 5, 2017.

197. Defendants have infringed and continue to infringe one or more claims, including at least Claim 1, of the '835 Patent.

198. Representative Claim 1 of the '835 Patent recites:

A seed, for implantation into a subject, comprising:

> a marker component configured to allow for the determination of the position of the seed within a target tissue,

> the marker component having a length extending along a centerline of the marker component between a first end and a second end and having a substantially continuous wall bounding a hollow interior; and
>
> a therapeutic, prophylactic, and/or diagnostic agent,
>
> wherein the agent is disposed within the hollow interior;
>
> wherein the length of the marker component is greater than the diameter of the hollow interior and
>
> wherein the substantially continuous wall includes at least one opening adapted to allow the agent to pass out of the hollow interior.

('835 Patent at 23:26–37.)

199. Claim 1 of the '835 Patent recites in part, "[a] seed, for implantation into a subject…" ('835 Patent at 23:26.) Defendants' Nexplanon product satisfies this claim limitation.

200. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants' Nexplanon product is a "rod shaped implant" which is "4 cm in length with a diameter of 2 mm…." (Nexplanon Prescribing Information at 1, 19).

201. In one embodiment, the '835 Patent describes "seeds shaped into a cylinder (or rod) having a diameter of between about 0.8 to 3 millimeters and a length of up to 40 millimeters [4cm]…." ('835 Patent at 14:31–35).

202. The diameter of Nexplanon (2 mm) is between 0.8 and 3 mm, and the length of Nexplanon (4 cm) is equivalent to 40 mm.

203. Nexplanon is implanted into subjects, e.g., for use as a contraceptive. (Nexplanon Prescribing Information at 1.)

204. Accordingly, Nexplanon may be considered, among other things, a seed for implantation in a subject.

205. Claim 1 of the ’835 Patent recites in part, “a marker component configured to allow for the determination of the position of the seed within a target tissue…” (’835 Patent at 23:26–28.) Defendants’ Nexplanon product satisfies this claim limitation.

206. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), the Nexplanon implant is comprised of “an ethylene vinyl acetate (EVA) copolymer core, containing 68 mg of the synthetic progestin etonogestrel, barium sulfate (radiopaque ingredient), and may also contain magnesium stearate, surrounded by an EVA copolymer skin.” (Nexplanon Prescribing Information at 19.)

207. Thus, the marker component is comprised of the EVA copolymer core, which contains barium sulfate (a radiopaque ingredient), and the EVA copolymer skin, which surrounds the EVA copolymer core.

208. The Nexplanon Prescribing Information recites the following: “[i]nsert one NEXPLANON subdermally just under the skin at the inner side of the non-dominant upper arm.” (Nexplanon Prescribing Information at 1); “[a]lways verify the presence of the implant in the woman’s arm immediately after insertion by palpation.” (Nexplanon Prescribing Information at 6); “[i]f the rod is not palpable…[u]se other methods to confirm the presence of the implant. Given the radiopaque nature of the implant, suitable methods for localization are two-dimensional X-ray and X-ray computerized tomography (CT scan)” (Nexplanon Prescribing Information at 7).

209. Accordingly, the marker component is configured to allow for the determination of the position of the Nexplanon product (the seed) within a target tissue.

210. Claim 1 of the '835 Patent recites in part, "the marker component having a length extending along a centerline of the marker component between a first end and a second end and having a substantially continuous wall bounding a hollow interior…" ('835 Patent at 23:28–32.) Defendants' Nexplanon product satisfies this claim limitation.

211. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants' Nexplanon product is "rod shaped" (Nexplanon Prescribing Information at 1.)

212. Defendants' Nexplanon product is comprised of an EVA copolymer core, "surrounded by an EVA copolymer skin." (Nexplanon Prescribing Information at 19.)

213. The EVA copolymer skin and the EVA copolymer core (marker component) is rod-shaped. (Nexplanon Prescribing Information at 1, 19.)

214. The rod-shaped marker component has a length extending along a centerline of the marker component. (Nexplanon Prescribing Information at 1, 19.)

215. The rod-shaped marker component has a first end and a second end. (Nexplanon Prescribing Information at 1, 19.)

216. The '037 Patent, which discloses Defendants' Nexplanon product, describes the "[p]reparation of a two layered implant … consisting of the core and a skin layer of EVA-14 copolymer." ('037 Patent at 5:8–14.)

217. The EVA copolymer skin surrounding the EVA copolymer core forms or is part of a substantially continuous wall.

218. Since the EVA copolymer skin surrounds the EVA copolymer core, the EVA copolymer skin would bound an interior (hollow) space.

219. Thus, the marker component has a length extending along a centerline of the marker component between a first end and a second end, and the EVA copolymer skin of the marker component has or forms part of a substantially continuous wall bounding an interior (hollow) space.

220. Claim 1 of the '835 Patent recites in part, "a therapeutic, prophylactic, and/or diagnostic agent…" ('835 Patent at 23:32–34.) Defendants' Nexplanon product satisfies this claim limitation.

221. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants' Nexplanon product is comprised of "68 mg of the synthetic progestin etonogestrel," which has been found by the FDA to be safe and efficacious in preventing pregnancy. (Nexplanon Prescribing Information at 1, 19.)

222. Thus, Defendants' Nexplanon product is comprised of a therapeutic and/or prophylactic agent (etonogestrel).

223. Claim 1 of the '835 Patent recites in part, "wherein the agent is disposed within the hollow interior…" ('835 Patent at 23:32–34.) Defendants' Nexplanon product satisfies this claim limitation.

224. Defendants' Nexplanon product is comprised of an "EVA copolymer core, containing 68 mg of the synthetic progestin etonogestrel, barium sulfate (radiopaque ingredient), and may also contain magnesium stearate, surrounded by an EVA copolymer skin." (Nexplanon Prescribing Information at 19.)

225. The EVA copolymer core contains a biocompatible component (EVA), a radiopaque marker (barium sulfate), and a therapeutic agent (etonogestrel). (Nexplanon Prescribing Information at 19.)

226. Accordingly, the agent (etonogestrel) is disposed within the interior (hollow) space, bounded at least in part by the EVA copolymer skin of the marker component.

227. Claim 1 of the '835 Patent recites in part, "wherein the length of the marker component is greater than the diameter of the hollow interior…" ('835 Patent at 23:34–35.) Defendants' Nexplanon product satisfies this claim limitation.

228. As shown by at least the Nexplanon Prescribing Information (revised 12/2016) and the Nexplanon FDA-Approved Patient Labeling (revised 03/2016), Defendants' Nexplanon product is a "rod shaped implant" which is "4 cm in length with a diameter of 2 mm…." (Nexplanon Prescribing Information at 1, 19.)

229. Accordingly, the length of Defendants' Nexplanon product (4 cm) is greater than the diameter of its interior (no more than 2 mm).

230. Defendants' Nexplanon product is comprised of an EVA copolymer core, "surrounded by an EVA copolymer skin." (Nexplanon Prescribing Information at 19.)

231. The marker component of Nexplanon has the same aspect ratio as the Nexplanon product.

232. For example, Example 1 of the '037 Patent, describes the "[p]reparation of a two layered implant … consisting of the core and a skin layer of EVA-14 copolymer." ('037 Patent at 5:8–14.)

233. Example 1 of the '037 Patent further recites, "[e]xtrusion lead to a co-axial fiber with a diameter of 2 mm and a skin thickness of 60 μm." ('037 Patent at 5:34–35.)

234. Thus, the interior (hollow) space, bounded at least in part by the EVA copolymer skin of the marker component, has a diameter of no more than 2 mm.

235. Moreover, the '037 Patent recites, "[t]he coaxial fiber was cut into 4.0 cm rods using a semiautomatic cutter (Diosynth or equivalent)." ('037 Patent at 5:37–38.)

236. Thus, the length of the marker component, which is comprised of the EVA copolymer skin and the EVA copolymer core, is 4 cm, which is equivalent to 40 mm.

237. Thus, accounting for the thickness of the EVA copolymer skin, the length of the marker component (40 mm) is greater than the diameter of the interior (hollow) space (no more than 2 mm).

238. Claim 1 of the '835 Patent recites in part, "wherein the substantially continuous wall includes at least one opening adapted to allow the agent to pass out of the hollow interior…" ('835 Patent at 23:35–37.) Defendants' Nexplanon product satisfies this claim limitation.

239. The '037 Patent, which discloses Defendants' Nexplanon product recites, "[i]t can therefore be concluded that no or hardly any barium sulphate crystals migrated out of the implant through the open ends." ('037 Patent at 9:4–6.)

240. The Nexplanon Prescribing Information recites, "[a]fter subdermal insertion of the etonogestrel implant, etonogestrel is released into the circulation and is approximately 100% bioavailable." (Nexplanon Prescribing Information at 19.)

241. Accordingly, Defendants' Nexplanon product includes at least one opening in its substantially continuous wall which allows the therapeutic agent to migrate out of the implant.

242. Defendants directly infringe (literally or under the doctrine of equivalents) and/or indirectly infringe (by inducement or contributorily) the claims of the '835 Patent before the

expiration thereof, including but not limited to, representative Claim 1 and Claims 3–4, 14, 16–17.

243. Defendants' Nexplanon product is accompanied by the Nexplanon Prescribing Information, directed primarily to health-care providers, as well as the FDA-Approved Patient Labeling, directed primarily to patients. (*See, e.g.*, **Exhibits F and G**.)

244. The Nexplanon Prescribing Information expressly encourages and instructs healthcare providers to use Defendants' Nexplanon product in their patients.

245. The FDA-Approved Patient Labeling expressly encourages use of Defendants' Nexplanon product by patients under the direction of a healthcare provider.

246. Thus, a patient and/or healthcare provider, following the Nexplanon Prescribing Information and/or FDA-Approved Patient Labeling, will infringe the '835 Patent by using Defendants' Nexplanon product.

247. Defendants know or should reasonably know that distributing the Nexplanon Prescribing Information and FDA-Approved Patient Labeling with Nexplanon will induce healthcare providers and/or patients to use Defendants' Nexplanon product, or contribute to an infringing use of Defendants' Nexplanon product.

248. Defendants, as well as patients and healthcare providers following the Nexplanon Prescribing Information or FDA-Approved Patient Labeling, directly and/or indirectly infringe literally and/or under the doctrine of equivalents, the '835 Patent.

249. Neither Nexplanon nor the use of Nexplanon according to the Nexplanon Prescribing Information are a staple article or commodity of commerce suitable for substantial noninfringing use.

250. Microspherix has been and continues to be damaged by Defendants infringement of the ’835 Patent.

PRAYER FOR RELIEF

WHEREFORE, Microspherix respectfully requests that this Court enter judgment in its favor against Defendants, and grant the following relief:

A. Judgment that Defendants directly and/or indirectly infringe literally and/or under the doctrine of equivalents, at least one claim of the ’402, ’401 and ’835 Patents;

B. Judgment that the ’402, ’401 and ’835 Patents have not been proven invalid or unenforceable;

C. A preliminary and/or permanent injunction that enjoins Defendants, their officers, partners, agents, servants, employees, attorneys, affiliates, divisions, subsidiaries, other related business entities, and those persons in active concert or participation with any of them from infringing the ’402, ’401 and/or ’835 Patents, or contributing to or inducing anyone to do the same, by acts including the manufacture, use, offer to sell, sale, distribution, or importation of any current or future versions of a product that infringes, or the use or manufacture of which infringes the ’402, ’401 and/or ’835 Patents;

D. An award to Microspherix of damages adequate to compensate it for Defendants’ past infringement and any continuing or future infringement including interest, costs, and disbursements as justified under 35 U.S.C. § 284;

E. A declaration that this an exceptional case and an award to Microspherix of its reasonable attorneys’ fees and expenses, as provided by 35 U.S.C. §§ 271(e)(4) and 285; and

F. Such other and further relief in law or equity as the Court deems just and appropriate.

DEMAND FOR JURY TRIAL

Microspherix hereby demands a trial by jury on all issues so triable.

* * *

Dated: June 30, 2021

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULE 11.2

Pursuant to Local Civil Rule 11.2, I hereby certify, to the best of my knowledge, that the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: June 30, 2021

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EXHIBIT A

National Drug Code Directory

The Drug Listing Act of 1972 requires registered drug establishments to provide the Food and Drug Administration (FDA) with a current list of all drugs manufactured, prepared, propagated, compounded, or processed by it for commercial distribution. (See Section 510 of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. § 360)). Drug products are identified and reported using a unique, three-segment number, called the National Drug Code (NDC), which serves as a universal product identifier for drugs. FDA publishes the listed NDC numbers and the information submitted as part of the listing information in the NDC Directory which is updated daily.

0052-0274-80 Nexplanon

Labeler Name	Organon USA Inc.	Name of Company corresponding to the labeler code segment of the ProductNDC.
NDC Code	0052-0274-80	The labeler code, product code, and package code segments of the National Drug Code number, separated by hyphens. Asterisks are no longer used or included within the product and package code segments to indicate certain configurations of the NDC.
Proprietary Name	Nexplanon	Also known as the trade name. It is the name of the product chosen by the labeler.
11 Digit NDC Code	00052-0274-80	It should be noted that many NDCs are displayed on drug packaging in a 10-digit format. Proper billing of an NDC requires an 11-digit number in a 5-4-2 format. Converting NDCs from a 10-digit to 11-digit format requires a strategically placed zero, dependent upon the 10-digit format.
Product NDC	0052-0274	The labeler code and product code segments of the National Drug Code number, separated by a hyphen. Asterisks are no longer used or included within the product code segment to indicate certain configurations of the NDC.
Product Type Name	HUMAN PRESCRIPTION DRUG	Indicates the type of product, such as Human Prescription Drug or Human OTC Drug. This data element corresponds to the “Document Type” of the SPL submission for the listing. The complete list of codes and translations can be found at www.fda.gov/edrls under Structured Product Labeling Resources.
Non Proprietary Name	etonogestrel	Sometimes called the generic name, this is usually the active ingredient(s) of the product.
Package Description	1 BLISTER PACK in 1 CARTON (0052-0274-80) > 1 IMPLANT in 1 BLISTER PACK	A description of the size and type of packaging in sentence form. Multilevel packages will have the descriptions concatenated together. For example: 4 BOTTLES in 1 CARTON/100 TABLETS in 1 BOTTLE.
Marketing Category Name	NDA	Product types are broken down into several potential Marketing Categories, such as NDA/ANDA/BLA, OTC Monograph, or Unapproved Drug. One and only one Marketing Category may be chosen for a product, not all marketing categories are available to all product types. Currently, only final marketed product categories are included. The complete list of codes and translations can be found at www.fda.gov/edrls under Structured Product Labeling Resources.
Application Number	NDA021529	This corresponds to the NDA, ANDA, or BLA number reported by the labeler for products which have the corresponding Marketing Category designated. If the designated Marketing Category is OTC Monograph Final or OTC Monograph Not Final, then the Application number will be the CFR citation corresponding to the appropriate Monograph (e.g. “part 341”). For unapproved drugs, this field will be null.

Start Marketing Date	20060717	This is the date that the labeler indicates was the start of its marketing of the drug product.
Dosage Form Name	IMPLANT	The translation of the DosageForm Code submitted by the firm. The complete list of codes and translations can be found www.fda.gov/edrls under Structured Product Labeling Resources.
Route Name	SUBCUTANEOUS	The translation of the Route Code submitted by the firm, indicating route of administration. The complete list of codes and translations can be found at www.fda.gov/edrls under Structured Product Labeling Resources.
Substance Name	ETONOGESTREL	This is the active ingredient list. Each ingredient name is the preferred term of the UNII code submitted.
Strength Number	68	These are the strength values (to be used with units below) of each active ingredient, listed in the same order as the SubstanceName field above.
Strength Unit	mg/1	These are the units to be used with the strength values above, listed in the same order as the SubstanceName and SubstanceNumber.
Pharmaceutical Classes	Progesterone Congeners [Chemical/Ingredient],Progestin [EPC]	These are the reported pharmaceutical class categories corresponding to the SubstanceNames listed above.
Status	Actual	Status
Last Update	2017-06-08	The date that a record was last updated or changed.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance, Immediate Office
Drug Registration and Listing Team
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
Email: eDRLS@fda.hhs.gov

For all questions regarding this bundle please contact Support@HIPAASpace.com. Also feel free to let us know about any suggestions or concerns. All additional information as well as customer support is available at http://www.HIPAASpace.com.

EXHIBIT B

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021529/S-015

SUPPLEMENT APPROVAL

Organon USA Inc., a subsidiary of Merck & Co., Inc.
Attention: Tonja W. Hampton, M.D.
Director, Global Regulatory Affairs
P.O. Box 2000
Rahway, NJ 07065

Dear Dr. Hampton:

Please refer to your Supplemental New Drug Application (sNDA) dated and received April 12, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Implanon and Nexplanon (etonogestrel implants).

This Prior Approval supplemental new drug application provides for changes to the Prescribing Information (PI) for Implanon and Nexplanon to update the 1) Warnings and Precautions Section, subsection, Return to Ovulation, 2) Drug Interactions Section, subsections, Effects of Other Drugs on Hormonal Contraceptives AND Effects of Hormonal Contraceptives on Other Drugs, 3) Use in Specific Populations Section, subsections Pregnancy AND Lactation, and 4) Patient Counseling Information Section.

Additionally, it includes changes to the Patient Package Insert (PPI) for Implanon and Nexplanon to update the Interaction with Other Medicines Section.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HYLTON V JOFFE
05/19/2017

EXHIBIT C

US009636402B2

(12) **United States Patent**
Kaplan

(10) **Patent No.: US 9,636,402 B2**
(45) **Date of Patent: *May 2, 2017**

(54) **FLEXIBLE AND/OR ELASTIC BRACHYTHERAPY SEED OR STRAND**

(71) Applicant: **Microspherix LLC**, Boca Raton, FL (US)

(72) Inventor: **Edward J. Kaplan**, Boca Ratan, FL (US)

(73) Assignee: **Microspherix LLC**, Boca Raton, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/711,658**

(22) Filed: **May 13, 2015**

(65) **Prior Publication Data**

US 2015/0238661 A1 Aug. 27, 2015

Related U.S. Application Data

(63) Continuation of application No. 14/473,159, filed on Aug. 29, 2014, which is a continuation of application No. 13/916,916, filed on Jun. 13, 2013, now Pat. No. 8,821,835, which is a continuation of application No. 12/823,700, filed on Jun. 25, 2010, now Pat. No. 8,470,294, which is a continuation of application No. 10/665,793, filed on Sep. 19, 2003, now Pat. No. 7,776,310, which is a continuation-in-part of application No. 09/861,196, filed on May 18, 2001, now Pat. No. 6,514,193, and a continuation-in-part of application No. 09/861,326, filed on May 18, 2001, now Pat. No. 6,746,661.

(60) Provisional application No. 60/412,050, filed on Sep. 19, 2002, provisional application No. 60/249,128, filed on Nov. 16, 2000.

(51) **Int. Cl.**

A61L 31/14	(2006.01)
A61L 31/10	(2006.01)
A61K 41/00	(2006.01)
A61K 47/48	(2006.01)
A61K 49/04	(2006.01)
A61K 51/12	(2006.01)
A61N 5/10	(2006.01)
A61K 49/00	(2006.01)
A61B 5/06	(2006.01)
A61L 31/16	(2006.01)
A61L 31/18	(2006.01)
A61B 90/00	(2016.01)

(52) **U.S. Cl.**

CPC ***A61K 41/0038*** (2013.01); ***A61B 5/064*** (2013.01); ***A61B 90/39*** (2016.02); ***A61K 47/48992*** (2013.01); ***A61K 49/00*** (2013.01); ***A61K 49/0409*** (2013.01); ***A61K 51/1282*** (2013.01); ***A61L 31/10*** (2013.01); ***A61L 31/146*** (2013.01); ***A61L 31/148*** (2013.01); ***A61L 31/16*** (2013.01); ***A61L 31/18*** (2013.01); ***A61N 5/1007*** (2013.01); ***A61N 5/1027*** (2013.01); *A61B 2090/3966* (2016.02); *A61L 2300/44* (2013.01); *A61N 2005/1023* (2013.01); *A61N 2005/1024* (2013.01)

(58) **Field of Classification Search**

CPC A61K 49/00; A61K 51/00

See application file for complete search history.

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Primary Examiner — Michael G Hartley

Assistant Examiner — Jagadishwar Samala

(74) *Attorney, Agent, or Firm* — Pabst Patent Group LLP

(57) **ABSTRACT**

A flexible or elastic brachytherapy strand that includes an imaging marker and/or a therapeutic, diagnostic or prophylactic agent such as a drug in a biocompatible carrier that can be delivered to a subject upon implantation into the subject through the bore of a brachytherapy implantation needle has been developed. Strands can be formed as chains or continuous arrays of seeds up to 50 centimeters or more, with or without spacer material, flaccid, rigid, or flexible.

19 Claims, 6 Drawing Sheets

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FIG. 1

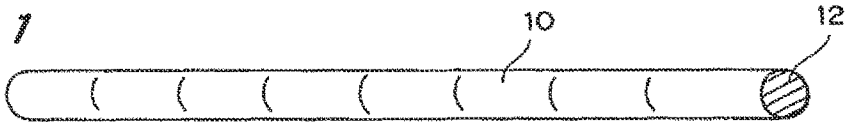


FIG. 2

FIG. 3A

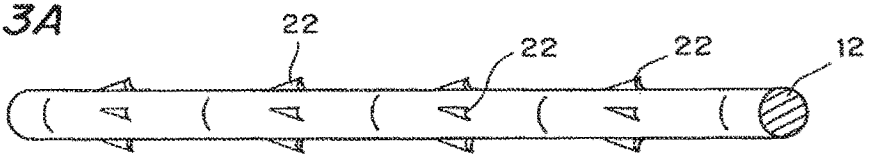


FIG. 3B

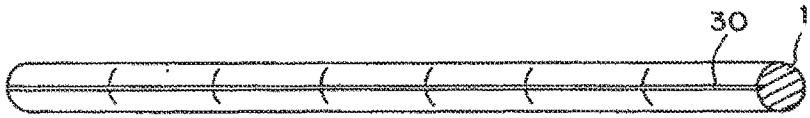


FIG. 3C

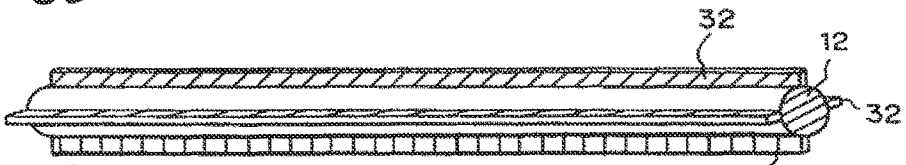


FIG. 3D

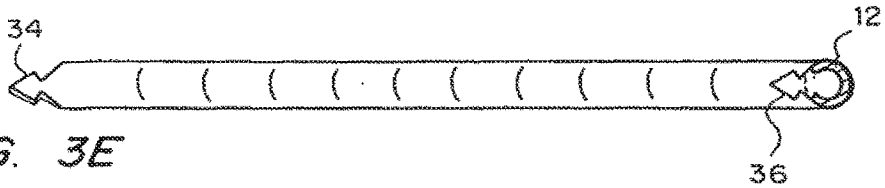
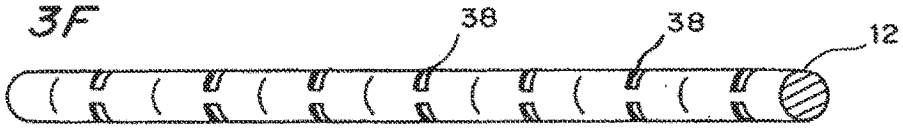


FIG. 3E

FIG. 3F



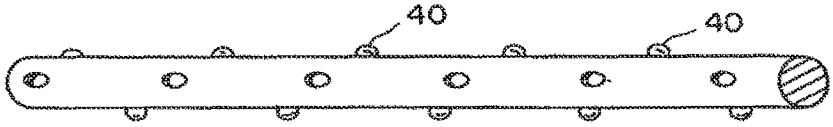


FIG. 3G

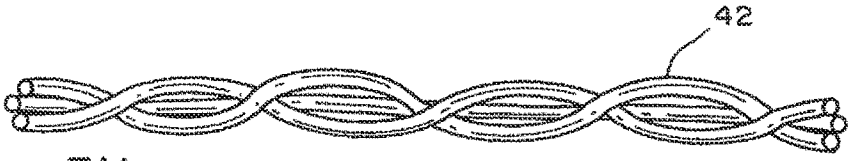


FIG. 3H

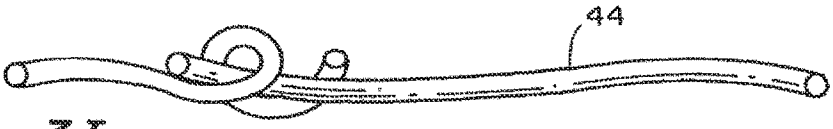


FIG. 3I

FIG. 4A

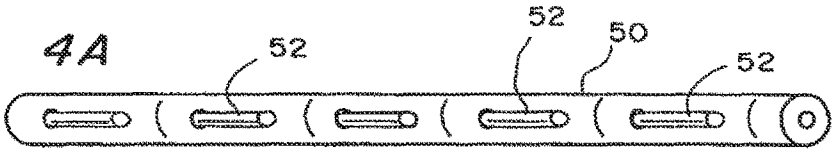


FIG. 4B

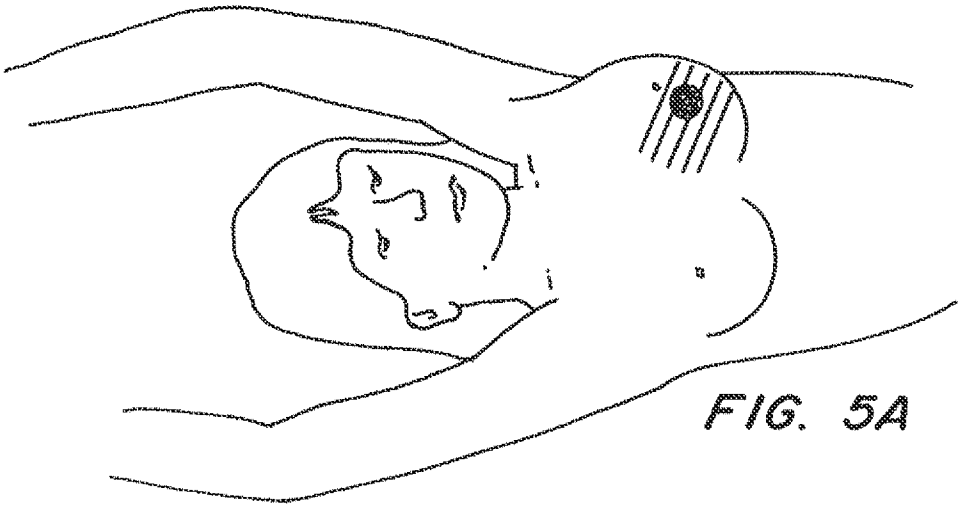


FIG. 5A

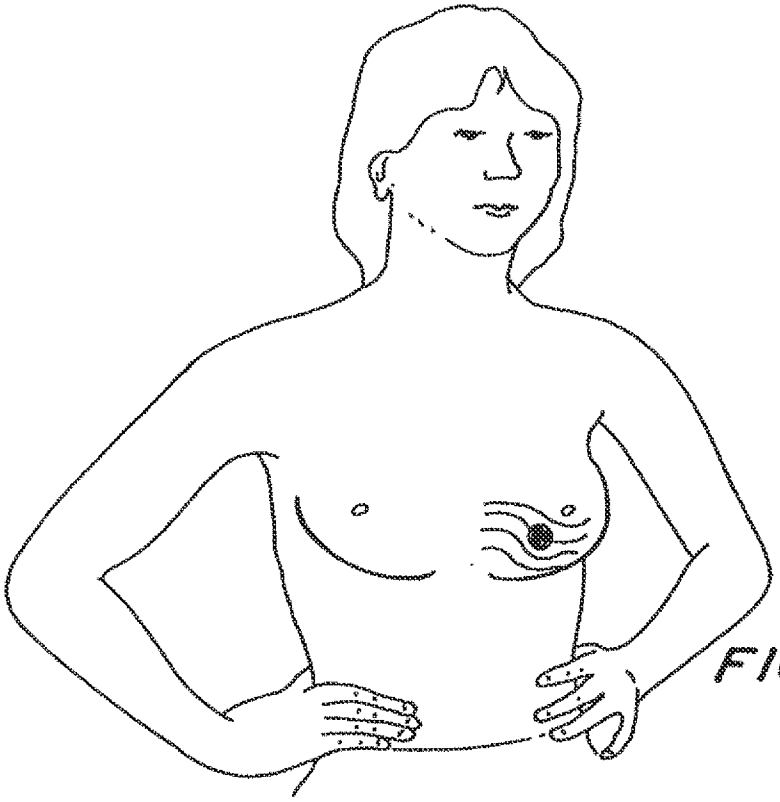


FIG. 5B

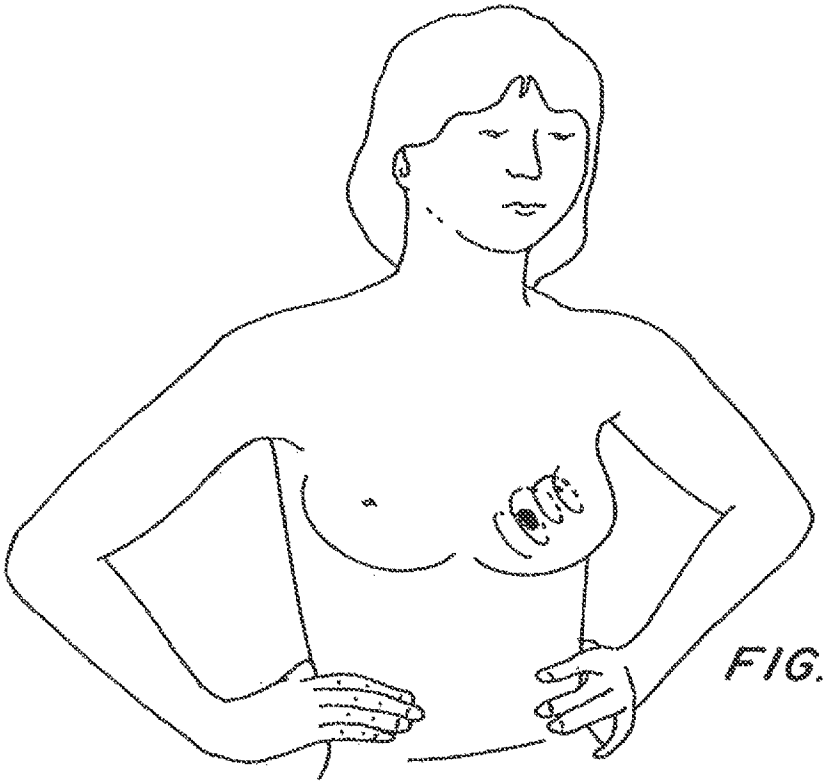


FIG. 5C

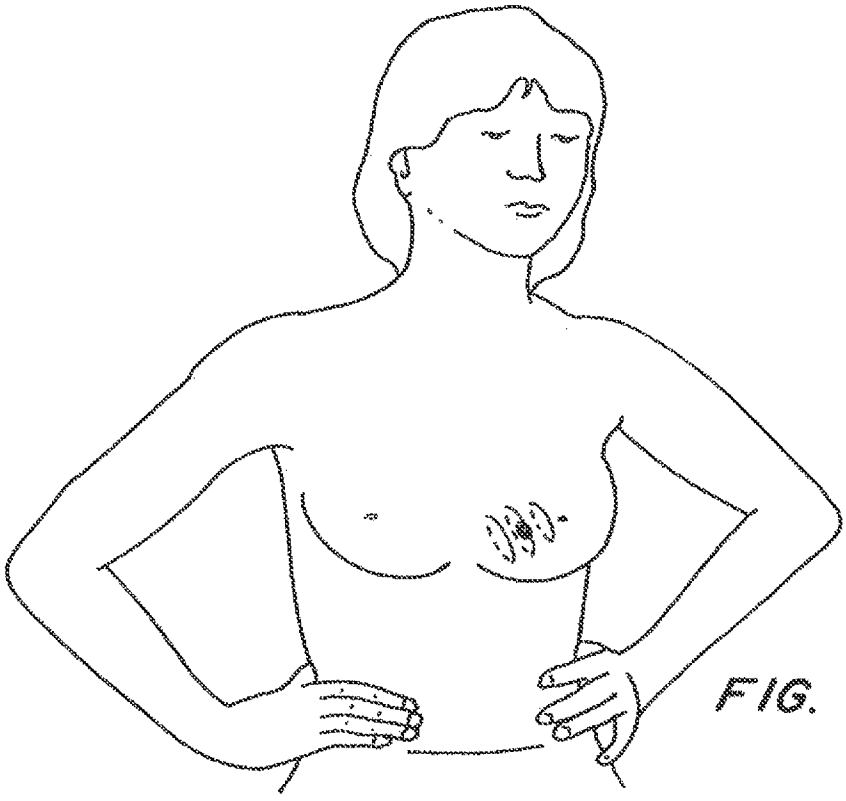
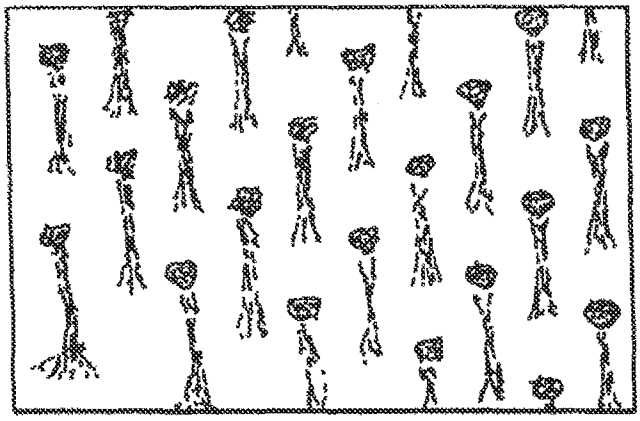


FIG. 5D

FIG. 6



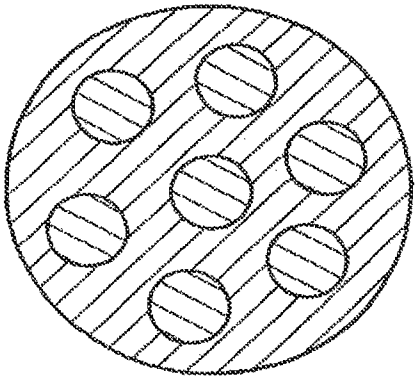


FIG. 7A

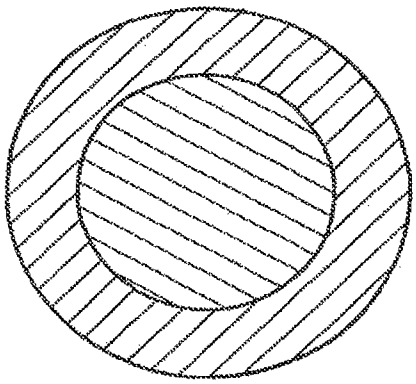


FIG. 7B

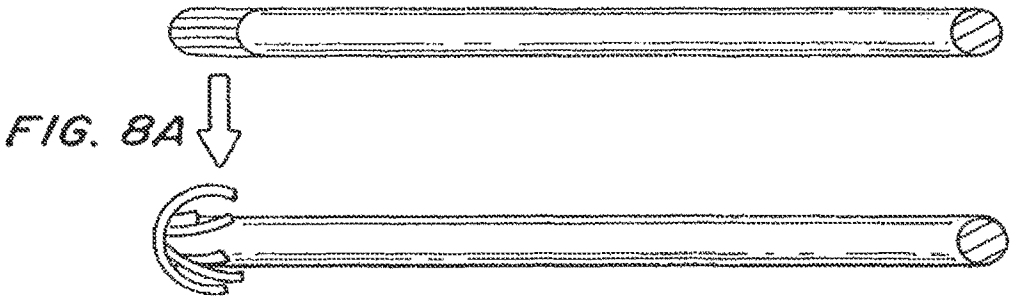


FIG. 8A

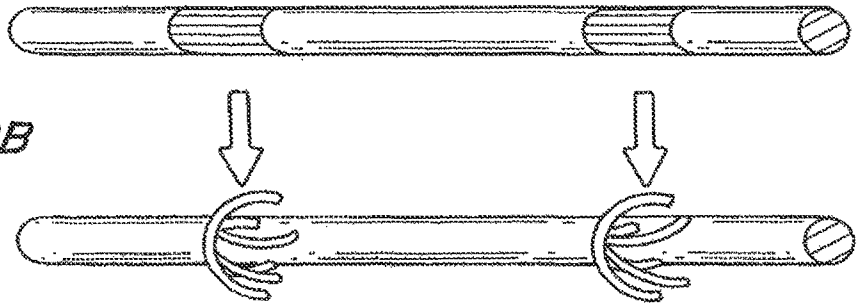


FIG. 8B

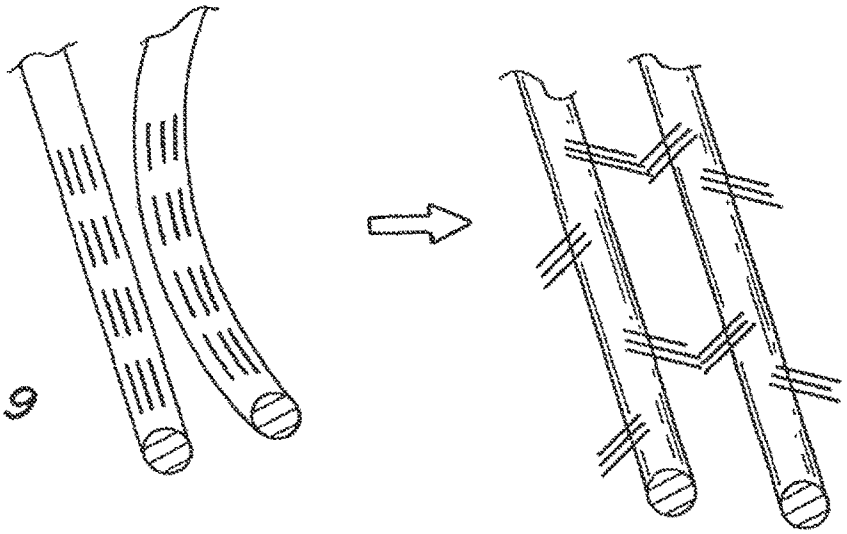


FIG. 9

FLEXIBLE AND/OR ELASTIC BRACHYTHERAPY SEED OR STRAND

BACKGROUND OF THE INVENTION

The present application is a continuation of U.S. application Ser No. 14/473,159, filed Aug. 29, 2014, entitled "Flexible and/or Elastic Brachytherapy Seed or Strand", by Edward J. Kaplan, which is a continuation of U.S. application Ser No. 13/916,916, filed Jun. 13, 2013, now U.S. Pat. No. 8,821,835, issued Sep. 2, 2014, which is a continuation of U.S. application Ser No. 12/823,700, filed Jun. 25, 2010, now U.S. Pat. No. 8,470,294, issued Jun. 25, 2013, which is a continuation of U.S. application Ser No. 10/665,793, filed Sep. 19, 2003, now U.S. Pat. No. 7,776,310, issued Aug. 17, 2010, which claims priority to and benefit of U.S. Provisional Application No. 60/412,050, filed Sep. 19, 2002, and is a continuation-in-part of U.S. Ser. No. 09/861,326 filed May 18, 2001, now U.S. Pat. No. 6,746,661, issued Jun. 8, 2004, which claims priority to and benefit of U.S. Provisional Application No. 60/249,128 filed Nov. 16, 2000, and U.S. application Ser. No. 10/665,793, filed Sep. 19, 2003, now U.S. Pat. No. 7,776,310, issued Aug. 17, 2010 is also a continuation-in-part of U.S. Ser. No. 09/861,196 filed May 18, 2001, now U.S. Pat. No. 6,514,193, issued Feb. 4, 2003, which claims priority to and benefit of U.S. provisional application 60/249,128 filed Nov. 16, 2000.

This application relates to imagable implantable brachytherapy devices, and methods of use thereof.

Radioactive seed therapy, commonly referred to as brachytherapy, is an established technique for treating various medical conditions, most notably prostate cancer. In a typical application of brachytherapy for treating prostate cancer, about 50-150 small seeds containing a radioisotope that emits a relatively short-acting type of radiation are surgically implanted in the diseased tissue. Because the seeds are localized near the diseased tissue, the radiation they emit is thereby concentrated on the cancerous cells and not on distantly located healthy tissue. In this respect, brachytherapy is advantageous over conventional external beam radiation.

A number of devices have been employed to implant radioactive seeds into tissues. See, e.g., U.S. Pat. No. 2,269,963 to Wappler; U.S. Pat. No. 4,402,308 to Scott; U.S. Pat. No. 5,860,909 to Mick; and U.S. Pat. No. 6,007,474 to Rydell. In a typical protocol for treating prostate cancer, an implantation device having a specialized needle is inserted through the skin between the rectum and scrotum into the prostate to deliver radioactive seeds to the prostate. The needle can be repositioned or a new needle used for other sites in the prostate where seeds are to be implanted. Typically, 20-40 needles are used to deliver between about 50-150 seeds per prostate. A rectal ultrasound probe is used to track the position of the needles. Once the end of a given needle is positioned in a desired location, a seed is forced down the bore of the needle so that it becomes lodged at that location.

As the seeds are implanted in the prostate as desired, the needles are removed from the patient. Over the ensuing several months the radiation emitted from the seeds kills the cancerous cells. Surgical removal of the seeds is usually not necessary because the type of radioisotope generally used decays over the several month period so that very little radiation is emitted from the seeds after this time. Currently marketed radioactive seeds take the form of a capsule encapsulating a radioisotope. See, e.g., Symmetra® I-125 (Bebig GmbH, Germany); IoGold™ I-125 and IoGold™ Pd-103 (North American Scientific, Inc., Chatsworth, Calif.); Best® I-125 and Best® Pd-103 (Best Industries, Springfield, Va.); Brachyseed® I-125 (Draximage, Inc., Canada); Intersource® Pd-103 (International Brachytherapy, Belgium); Oncoseed® I-125 (Nycomed Amersham, UK); STM 1250 I-125 (Sourcetech Medical, Carol Steam, Ill.); Pharmaseed® I-125 (Syncor, Woodland Hills, Calif.); Prostaseed™ I-125 (Urocor, Oklahoma City, Okla.); and I-plant® I-125 (Implant Sciences Corporation, Wakefield, Mass.). The capsule of these seeds is made of a biocompatible substance such as titanium or stainless steel, and is tightly sealed to prevent leaching of the radioisotope. The capsule is sized to fit down the bore of one of the needles used in the implantation device. Since most such needles are about 18 gauge, the capsule typically has a diameter of about 0.8 mm and a length of about 4.5 mm.

The two radioisotopes most commonly used in prostate brachytherapy seeds are iodine (I-125) and palladium (Pd-103). Both emit low energy irradiation and have half-life characteristics ideal for treating tumors. For example, I-125 seeds decay at a rate of 50% every 60 days, so that at typical starting doses their radioactivity is almost exhausted after ten months. Pd-103 seeds decay even more quickly, losing half their energy every 17 days so that they are nearly inert after only 3 months.

Radioactive brachytherapy seeds may also contain other components. For example, to assist in tracking their proper placement using standard X-ray imaging techniques, seeds may contain a radiopaque marker. Markers are typically made of high atomic number (i.e., "high Z") elements or alloys or mixtures containing such elements. Examples of these include platinum, iridium, rhenium, gold, tantalum, lead, bismuth alloys, indium alloys, solder or other alloys with low melting points, tungsten, and silver. Many radiopaque markers are currently being marketed. Examples include platinum/iridium markers (Draximage, Inc. and International Brachytherapy), gold rods (Bebig GmbH), gold/copper alloy markers (North American Scientific), palladium rods (Syncor), tungsten markers (Best Industries), silver rods (Nycomed Amersham), silver spheres (International Isotopes Inc. and Urocor), and silver wire (Implant Sciences Corp.). Other radiopaque markers include polymers impregnated with various substances (see, e.g., U.S. Pat. No. 6,077,880).

A number of different U.S. patents disclose technology relating to brachytherapy. For example, U.S. Pat. No. 3,351,049 to Lawrence discloses the use of a low-energy X-ray-emitting interstitial implant as a brachytherapy source. In addition, U.S. Pat. No. 4,323,055 to Kubiatowicz; U.S. Pat. No. 4,702,228 to Russell; U.S. Pat. No. 4,891,165 to Suthanthiran; U.S. Pat. No. 5,405,309 to Carden; U.S. Pat. No. 5,713,828 to Coniglione; U.S. Pat. No. 5,997,463 to Cutrer; U.S. Pat. No. 6,066,083 to Slater; and U.S. Pat. No. 6,074,337 to Tucker disclose technologies relating to brachytherapy devices.

The seeds have also been utilized to treat other types of cancers, such as pancreas, liver, lung and brain. For technical reasons, other organ systems or tissues are not amenable to this type of permanent seed implantation. These include hollow viscera such as the urinary bladder, mobile/muscular viscera such as the base of tongue, and tissues where a cavity or tumor bed has been created as a result of resection, as in the breast. In hollow viscera, loose seeds cannot be reliably spaced out owing to a dearth of tissue and the associated risk of losing the seeds into the lumen or cavity of the organ. Likewise in mobile/muscular and irregularly shaped viscera such as the base of tongue, loose seeds

cannot be spaced reliably, and strands of permanent seeds like those described in U.S. Pat. No. 4,754,745 to Horowitz or U.S. Pat. No. 5,322,499 to Liprie are still too inflexible to be used because of the metallic seeds that are embedded within them. Similarly, the wire coils described in U.S. Pat. No. 6,436,026 to Sioshansi, although flexible, are not meant to be implanted permanently and require a means of afterloading and removal.

The situation in breast cancer is similar to that of a hollow organ, whereby loose seeds are difficult to space properly, and may fall into the resection cavity, thus spoiling the dosimetry plan. Despite U.S. Patent application No. 20020087078 by Cox which describes the insertion of a radioactive seed into a breast with cancer, the seed is placed inside the actual breast cancer and is removed along with the tumor at the time of the cancer surgery. Therefore, in this instance, the radioactive seed is not meant to serve a therapeutic purpose. Breast tissue is also similar to the base of tongue or other mobile organs since the breast may be very generous and supple, conforming to forces of gravity or pressure. In fact, for these reasons, metallic seeds are not currently used for permanent therapeutic implantation into a breast.

In each of the above circumstances where use of permanent seeds is not desirable, temporary implants are generally used. This is accomplished via placement of afterloading devices such as the Henschke applicator for cervix cancer, hairpin needles for the base of tongue, and silastic catheters for breast cancer. Once the respective applicators have been placed, radioactive sources are loaded and remain indwelling for a prescribed finite period, usually hours to days. The sources and afterloading devices are then completely removed.

Disadvantages of these temporary systems are that patients often most stay in the hospital for the entire time that low dose rate sources are indwelling, or between radiotherapy fractions or sessions if high dose rate sources are used. In the case of afterloading catheters, the catheters are sutured in place for several days, causing acute pain, swelling, and possible infection or scarring. In the case of base of tongue implants, patients frequently require temporary tracheostomies to keep their airway open while the hairpin needles remain in place. In one new temporary high dose rate system by Proxima Therapeutics®, surgical placement of a balloon catheter is performed on the breast. The device has a catheter leading from the balloon in the tumor bed to the skin to provide ingress and egress for the temporary brachytherapy source. The balloon is deflated at the conclusion of several days of brachytherapy sessions, and is pulled out of the breast by hand.

It is an object of the present invention to provide biodegradable strands or other structures that are flexible and permanently implantable.

It is another object of the present invention to provide biodegradable strands or other structures that are flexible and implantable.

It is still another object of the present invention to provide non-polymeric biodegradable implantable seeds and a means for readily imaging implanted seeds.

It is also an object of the present invention to provide brachytherapy seeds and strands which can be used for other purposes, for example, drug delivery.

SUMMARY OF THE INVENTION

A brachytherapy strand that is elastic and/or flexible and preferably biodegradable has been developed. A drug or other therapeutically active substance or diagnostic can be included in the strand in addition to, or as an alternative to, a radioisotope. The rate of release in the implantation site can be controlled by controlling the rate of degradation and/or release at the implantation site. In the preferred embodiment, the strands also contain a radioopaque material or other means for external imaging. The flexible material may be polymeric or inorganic material. Strands can be formed as chains or continuous arrays of seeds up to 50 centimeters or more, with or without spacer material, flaccid, rigid, or flexible.

Like conventional radioactive brachytherapy seeds, the strands can be precisely implanted in many different target tissues without the need for invasive surgery. In the preferred embodiment, the strands are implanted into the subject through the bore of a brachytherapy implantation needle or catheter. The therapeutically active substance included within a strand can be delivered in a controlled fashion over a relatively long period of time (e.g., weeks, months, or longer periods). Since concentrations of the therapeutically active substance will be greater at the implantation site (e.g., the diseased tissue), any potential deleterious effect of the therapeutically active substance on healthy tissue located away from the implantation site will be reduced.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic side view of a cylindrically shaped brachytherapy strand.

FIG. **2** is a schematic side view of a hollow tube-shaped brachytherapy strand.

FIGS. **3**A-**3**I are strands with inert spacers, interspersed for cutting (FIG. **3**A); with pop-up wings to prevent migration or shifting alter implanting (FIG. **3**B); with a radiopaque strip fanning through it (FIG. **3**C); with cross-style stabilizers (FIG. **3**D); with male and female ends to facilitate joining, e.g., in a ring (FIG. **3**E); with indentations for cutting or breaking into smaller strands (FIG. **3**F); with a stabilizer, such as bumps (FIG. **3**G); a braided strand (FIG. **3**H); and strands knotted together (FIG. **3**I).

FIGS. **4**A and **4**B are a strand with radioactive seeds interspersed (perspective view, FIG. **4**A; cross-sectional view, FIG. **4**B).

FIGS. **5**A-**5**D are perspective views of strands after introduction into breast adjacent to lumpectomy site (larger circle) below the nipple (smaller circle) (FIG. **5**A); strands conforming to shape of breast with patient now upright, lumpectomy site is shown as larger black circle, nipple as smaller circle (FIG. **5**B); strand deployed as a coil (FIG. **5**C); and strands deployed as rings around lumpectomy site (FIG. **5**D).

FIG. **6** is a depiction of microfabricated polyimide hairs used as a coating for the brachytherapy seed or strand to impart adhesive properties.

FIGS. **7**A and **7**B are transverse cross-section views of a brachytherapy strand with multiple internal conduits (FIG. **7**A) or a single conduit (FIG. **7**B).

FIGS. **8**A and **8**B are depictions of a brachytherapy strand equipped with shape memory polymeric anchoring structures at the ends of the strand (FIG. **8**A) and interspersed along the length of the strand (FIG. **8**B), before and after deployment.

FIG. **9** is a depiction of a brachytherapy strand equipped with shape memory polymeric anchors positioned to brace or center the strands within irregularly shaped tissues.

DETAILED DESCRIPTION OF THE INVENTION

An elastic and/or flexible, and preferably biodegradable, brachytherapy seed or strand of seeds, has been developed. As used herein "elastic" refers to a material which has the ability to recover from relatively large deformations, or withstand them, or which can be elongated to multiple times its original length, without breaking. In one preferred embodiment, the brachytherapy strand includes a biocompatible component, a therapeutically active component that includes a non-radioactive drug, and in a more preferred embodiment, a radiopaque marker. The biocompatible component is physically associated with a therapeutically active component and in contact with the marker. In a second embodiment, the brachytherapy strand includes a non-metal biocompatible component, a therapeutically active component comprising a radioisotope, and a radiopaque or other diagnostic marker, the biocompatible component being (a) physically associated with a therapeutically active component and (b) in contact with the diagnostic marker, wherein the brachytherapy strand has a size and shape suitable for passing through the bore of a needle typically having an interior diameter of less than about 2.7 millimeters (10 gauge). In another embodiment, the biocompatible component is biodegradable.

Depending on the particular application, the brachytherapy strands offer other advantages. Among these, for example, compared to conventional systemic administration (e.g., oral or intravenous delivery) of therapeutically active substances, the brachytherapy strands can provide higher and more consistent concentrations of a therapeutically active substance to a target tissue. They can also eliminate the need for repeated injections as well as circumvent delivery problems such as where a target tissue lacks an intact vascular supply (e.g., a target tissue whose blood flow may be compromised) or is otherwise sequestered from the blood supply (e.g., via the blood-brain barrier of the central nervous system). In some embodiments of the strands that do not contain a radioisotope (e.g., those having only the therapeutically active substance and biodegradable component), after the therapeutically active substance is completely released and the biodegradable component is fully decomposed, no foreign device will remain at the implantation site.

I. Brachytherapy Strands.

Brachytherapy strands typically have a size and shape suitable for passing through the bore of a needle having an interior diameter of less than about 2.7 millimeters (10 gauge), less than about 1.4 millimeters (15 gauge), less than about 0.84 millimeters (18 gauge), or less than about 0.56 millimeters (24 gauge). In one version, the strand is shaped into a cylinder having a diameter of between about 0.5 to 3 millimeters and a length of 20, 30, 40 centimeters or more.

A. Materials for Making the Brachytherapy Seeds.

Any appropriate biocompatible material can be used to form the brachytherapy seeds. Preferred materials include polymeric materials which are approved by the Food and Drug Administration for implantation.

In the preferred embodiment, the seeds are formed of a biodegradable material. Examples of suitable materials include synthetic polymers such as polyhydroxyacids (polylactic acid, polyglycolic-lactic acid), polyanhydrides (poly(bis(p-carboxyphenoxy) propane anhydride, poly(bis(p-carboxy) methane anhydride), copolymer of polycarboxyphenoxypropane and sebacic acid); polyorthoesters; polyhydroxyalkanoates (polyhyroxybutyric acid); and poly(isobutylcyanoacrylate). Other examples include open cell polylactic acid; co-polymers of a fatty acid dimer and sebacic acid; poly(carboxyphenoxy) hexane; poly-1,4-phenylene dipropionic acid; polyisophthalic acid; polydodecanedioic acid; poly(glycol-sebacate) (PGS); or other polymers described below. See, e.g., Biomaterials Engineering and Devices: Human Applications: Fundamentals and Vascular and Carrier Applications, Donald L. Wise et al. (eds), Humana Press, 2000; *Biomaterials Science: An Introduction to Materials in Medicine*, Buddy D. Ratner et al. (eds.). Academic Press, 1997; and *Biomaterials and Bioengineering Handbook*, Donald L. Wise, Marcel Dekker, 2000.

These polymers can be obtained from sources such as Sigma Chemical Co., St, Louis, Mo.; Polysciences, Warrenton, Pa.; Aldrich, Milwaukee, Wis.; Fluka, Ronkonkoma, N.Y.; and BioRad, Richmond, Calif., or can be synthesized from monomers obtained from these or other suppliers using standard techniques.

In addition to synthetic polymers, natural polymers may also be used. In the preferred embodiment, the natural polymers are biodegradable. For example, tissue such as connective tissue from the walls of blood vessels or extracellular matrix may be used as a biodegradable carrier for delivery of radiation or another therapeutic substance. See, for example, U.S. Pat. No. 5,429,634 to Narcisco. Tissue may be autologous, heterologous, engineered, or otherwise modified so long as it is biocompatible with the target tissue. A patient may donate his own tissue to serve as a carrier for the therapeutic substance and/or radionuclide. Other tissues or natural polymers may serve as the degradable carrier matrices. For example, polysaccharides such as starch and dextran, proteins such as collagen, fibrin (Perka, et al., Tissue Eng. 7:359-361 (2001) and Senderoff, et al., J. Parenteral Sci. 45:2-6 (1991)), and albumin (see, for example, U.S. Pat. No. 5,707,644 to Ilum), elastin-like peptides, lipids, and combinations thereof. These materials can be derived from any of the sources known to those skilled in the art, including the patient's own tissues or blood.

Seeds or strands can also be made from synthetic or natural biocompatible non-polymeric and/or inorganic materials, which are preferably biodegradable. See for example, WO 99/53898 describing bioabsorbable porous silicon seeds and WO 00/50349 describing biodegradable ceramic fibers from silica sols. Other examples of non-polymeric and/or organic materials include: U.S. Pat. No. 5,640,705 to Koruga describing radiation-containing fullerene molecules; WO 02/34959A2 by Yeda Research and Development Co. Ltd. describing inorganic fullerene-like nanoparticles or structures; EP 1205437A1 to Osawa describing nano-size particulate graphite and multi-layer fullerene; U.S. Pat. No. 5,766,618 to Laurencin describing a polymeric-hydroxyapatite bone composite; GB 235140A to Asako Matsushima describing a ceramic composite such as hydroxyapatite for sustained release; and U.S. Pat. No. 5,762,950 to Antti Yli-Urpo disclosing a calcium phosphate, e.g. hydroxyapatite, bioactive ceramic for timed release.

In the case of radioactive seeds, it can be left to the clinician to select from any number of biodegradable carrier matrices which contain the radionuclide, so long as the degradation characteristics of the carrier substance are consistent with the desired absorption profile. This is because the carrier matrix itself will be sequestered from the surrounding target tissue along with the radionuclide until the radionuclide has decayed to an insignificant activity. At that time or afterwards, the biodegradable layer overlying the

radioactive matrix will be eroded away, thus beginning a similar process for the now non-radioactive or nearly spent radioactive carrier.

Strands may also be made of non-biodegradable materials, especially the radiopaque strand materials currently used to form beads for treatment of prostate cancer, although this is not as preferred as the biodegradable materials. As described above, the capsule (and as described herein, the strand) of these seeds is made of a biocompatible substance such as titanium or stainless steel, which is tightly sealed to prevent leaching of the radioisotope.

B. Radioactive Tracers

Optionally, brachytherapy seed or strand can be imparted with a means of tracing the radioactive contents should those contents be released inadvertently. Unforeseen problems associated with leakage of radioactive material, whether it be into the surrounding tissues in a patient, in a pathology lab, in a nuclear medicine lab, or in the operating room have been recently discovered as they relate to polymer seeds. The seed/strand should contain a means of tracing their contents should those contents be released inadvertently. This mechanism can rely on inclusion of fluorescent, luminescent, colored, pigmented or other approaches for tagging, detecting, or otherwise identifying the seed/strand contents either visually or with instrument assistance.

Fluorescence can be imparted using the appropriate polymer or other biodegradable substance, such as described by Sung in U.S. Pat. No. 4,885,254, Bryan in U.S. Pat. No. 6,416,960 B1, Barbera-Guillem in U.S. Pat. No. 6,548,171 B1, or Greiner in U.S. Patent Application No. 2003/0010508A1.

Luminescence can be imparted using the appropriate polymer or other biodegradable substance, such as described by Towns in WO01/49768 A2, Sakakibara in EP 1 311 138 A1, Bryan in U.S. Pat. No. 6,436,682B1, Hancock in U.S. Patent Application No. 2003/0134959A1, or Wood in U.S. Pat. No. 6,552,179B1. Bioluminescence materials are described in U.S. Pat. No. 5,670,356. In addition, chemiluminescent and electroluminescent substances might be utilized, as well as other types of luminescent substances as would be known to one skilled in the art.

Quantum dots may also be loaded into the seeds and utilized to locate spilled substances from ruptured seeds/strands, like those described in U.S. Patent Application No. 2003/0129311A1 or Dobson in WO 95/13891 (see also Jaiswal et al. *Nature Biotechnology* 2003; 21:47-51, and Quantum Dot Corporation's Qdot™ biotin conjugate).

Dyed biodegradable polymeric material may be used, as described by Burkhard in EP 1 093 824 A2. Other dyes can be used as indicated. Ultraviolet light can be utilized to detect a therapeutic agent like radioactive substances or drugs using a format described by Koshihara in U.S. Pat. No. 6,456,636 B1, or by Nakashima in WO 00/53659. Infrared dyes may be used, as described by Paulus in U.S. Pat. No. 5,426,143.

Those skilled in the art will be familiar with labeling, doping, or tagging the contents of the seeds/strands with agents that can be identified without modification, or pro-agents that can be identified by the addition of an activating substance or other means, such as labeled antibodies and the like.

C. Therapeutic and Diagnostic Agents

Polymers can be used to form, or to coat, drug delivery devices such as strands or strands containing any of a wide range of therapeutic and diagnostic agents. Any of a wide range of therapeutic, diagnostic and prophylactic materials can be incorporated into the strands, including organic compounds, inorganic compounds, proteins, polysaccharides, and nucleic acids, such as DNA, using standard techniques.

The non-radioactive drug can take the form of stimulating and growth factors; gene vectors; viral vectors; anti-angiogenesis agents; cytostatic, cytotoxic, and cytocidal agents; transforming agents; apoptosis-inducing agents; radiosensitizers; radioprotectants; hormones; enzymes; antibiotics; antiviral agents; mitogens; cytokines; anti-inflammatory agents; immunotoxins; antibodies; or antigens. For example, the non-radioactive therapeutic can be an anti-neoplastic agent such as paclitaxel, 5-fluorouracil, or cisplatin. It can also be a radiosensitizing agent such as 5-fluorouracil, etanidazole, tirapazamine, bromodeoxyuridine (BUdR) and iododeoxyuridine (IUdR).

Many different therapeutically active substances have been associated with biocompatible materials for use in drug delivery systems apart from brachytherapy strands. These include, for example, adriamycin (Moritera et al., *Invest. Ophthal. Vis. Sci.* 33:3125-30, 1992); bupivicaine (Park et al., *J. Controlled Release* 52:179-189, 1998); camptothecin (Weingart et al., *Int. J. Cancer* 62:1-5, 1995); carboplatin (Chen et al., *Drug Delivery* 4:301-11, 1997); carmustine (Brem et al., *J. Neurosurg* 74:441-6, 1991; and U.S. Pat. Nos. 4,789,724 and 5,179,189); cefazolin (Park et al., *J. Controlled Rel.* 52:179-189, 1998); cisplatin (Yapp et al., *IJROBP* 39:497-504, 1997); cortisone (Tamargo et al., *J. Neurooncol.* 9:131-8, 1990); cyclosporine (Sanchez et al., *Drug Delivery* 2:21-8, 1995); daunorubicin (Dash et al., *J. Pharmacol. Tox. Meth.* 40:1-12, 1999); dexamethasone (Reinhard et al., *J Contr. Rel.* 16:331-340, 1991); dopamine (During et al., *Ann Neurol.* 25:351-6, 1989); etanidazole (Yapp et al., *Radiotherapy Oncol.* 53:77-84, 1999); 5-fluorouracil (Menei et al., *Cancer* 86:325-30, 1999); fluconazole (Miyamoto et al., *Curr. Eye Res.* 16:930-5, 1997); 4-hydroxycyclophosphamide (Judy et al., *J. Neurosurg.* 82:481-6, 1995); ganciclovir (Kunou et al., *J. Controlled Rel.* 37: 143-150, 1995); gentamicin (Laurentin et al., *J. Orthopaed. Res.* 11:256-62, 1993); heparin (Tamargo et al., *J Neurooncol.* 9:131-8, 1990); interleukin-12 (Kuriakose et al., *Head & Neck* 22:57-63, 2000); naproxen (Conforti et al., *J. Pharm. Pharmacol.* 48:468-73, 1996); nerve growth factor (Camerata et al., *Neurosurgery* 30:313-19, 1992); retroviral vector producer cells to transfer a cytotoxic gene product (Beer et al. *Adv. Drug Deliver. Rev.* 27:59-66, 1997); taxol (Park et al., *J. Controlled Rel.* 52:179-189, 1998; and Harper, E et al., *Clin. Cancer Res.,* 5:4242-4248, 1999); tetanus toxoid (Alonso et al., *Vaccine* 12:299-306, 1994); tetracaine hydrochloride (Ramirez et al., *J. Microencap.* 16:105-15, 1999); tirapazamine (Yuan et al., *Radiation Oncol. Investig.* 7:218-30, 1999); thyrotropin-releasing hormone (Kubek et al., *Brain Res.* 809:189-97, 1998); and vaccines (Chattaraj et al., *J. Controlled Rel.* 58:223-32, 1999). Other therapeutically active substances that can be combined with a biocompatible component include: anesthetics, angiogenesis inhibitors (e.g., Lau D. H. et al., *Cancer Biother., Radiopharm.* 14:31-6, 1999), antibiotics (e.g., Bahk J. Y. et al., *J. Urol.* 163:1560-4, 2000; and Miyamoto H. et al., *Current Eye Research* 16:930-5, 1997), antibodies (e.g., Gomez S. M. et al., *Biotechnol. Prog.* 15:238-44, 1999), anticoagulants (e.g., Tamargo R. J. et al., J Neurooncol. 9:131-138, 1990), antigens (e.g., Machluf M. et al., J. Pharm. Sci. 89:1550-57, 2000), anti-inflammatory agents (e.g., Reinhard C. S. et al., J. Controlled Release 16:331-40, 1991; and Tamargo R. J. et al., J. Neurosurg. 74; 956-61, 1991), antivirals, apoptosis-inhibiting agents (e.g., Macias D. et al., Anat. Embryol. (Berl) 193:533-41, 1996),

cytokines (e.g., Edelman E. R. et al., Biomaterials 12:619-26, 1991), cytotoxic agents (e.g., Brem H. et al., J. Neurosurg. 80:283-90, 1994; Brem H. et al., J. Neurosurg. 80:283-90, 1094; Brem H. et al., Lancet 345:1008-12, 1995; Ewend M. G. et al., Cancer Res. 56:5217-23, 1996; Fung L. K. et al., Cancer Res. 58:672-85, 1998; Grossman S. et al., J. Neurosurg. 76:640-47, 1992; Kong Q. et al., J. Surgical Oncology 69:76-82, 1998; Shikani A. H. et al., Laryngoscope 110:907-17, 2000; Straw R. C. et al., J. Orthop. Res. 12:871-7, 1994; Tamargo R. J. et al., Cancer Research 53:329-33, 1993; Valtonen S. et al., Neurosurgery 41:44-9, 1997; Walter K. A. et al., Cancer Research 54:2207-12, 1994; Yapp D. T. T. et al., IJROBP 39:497-504, 1997; Yapp D. T. T. et al., Anti-Cancer Drugs 9:791-796, 1998; Yapp D. T. T. et al., IJROBP 42:413-20, 1998; and Yoshida M. et al., Biomaterials 10:16-22, 1989), enzymes (e.g., Park T. G. et al., J. Control Release 55:181-91, 1998), gene vectors (e.g., Hao T. et al., J. Control Release 69:249-59, 2000; and Maheshwari A. et al., Mol. Ther. 2:121-30, 2000), hormones (e.g., Rosa G. D. et al., J. Control Release 69:283-95, 2000), immunosuppressants (e.g., Sanchez A. et al., Drug Delivery 2:21-8, 1995), mitogens (e.g., Ertl B. et al., J. Drug Target 8:173-84, 2000), neurotransmitters (e.g., During M. J. et al., Ann Neurology 25:351-6, 1989), radioprotectants (e.g., Monig H. et al., Strahlenther Onkol. 166:235-41, 1990), radiosensitizers (e.g., Williams J. A., et al., IJROBP 42:631-39, 1998; and Cardinale R. M. et al., Radiat. Oncol. Invest. 6:63-70, 1998), stimulating and growth factors, transforming agents (e.g., Hong L. et al., Tissue Eng. 6:331-40, 2000), and viral vectors.

Various known methods and seeds relate to the application of heat to a target tissue for the purpose of killing cancerous cells (see for example Gordon in U.S. Pat. No. 4,569,836 and Delannoy in U.S. Pat. No. 5,284,144). Prior art metallic seeds known as "thermoseeds" have been described by Paulus in U.S. Pat. No. 5,429,583. In contrast to metal thermoseeds that generate heat mainly by eddy current loss, ferromagnetic microspheres generate heat predominantly by hysteresis loss.

Since it is widely known that clinically relevant heating of tissues can be generated by magnetic hysteresis effects, a preferred embodiment includes a magnetically imbued biodegradable carrier within the strands/seeds. Widder described an intravascular version of this kind of ferromagnetic microsphere in U.S. Pat. No. 4,247,406. Mitsumori et al. used a dextran-magnetite degradable starch microsphere in their work on inductive hyperthermia in rabbits (Mitsumori et al., *Int J Hyperthermia* 1994; 10:785-93) Minamimura et al. were the first investigator to show significant anti-tumor efficacy in tumor-bearing rats who were injected with dextran-magnetite microspheres that were then exposed to magnetic forces to generate heat within the tumors (Minamimura et al., *Int. J. Oncol.* 2000; 16:1153-8). Moroz et al. described successful beating of deep-seated soft tissue in pigs above the critical 42° C. therapeutic threshold following infusions of magnetic iron oxide-doped polymer microspheres (Moroz et al., *J. Surg. Res.* 2002; 105:209-14).

In addition to polymers and starch, other biodegradable substrates can be incorporated into the seeds described herein, as desired by those skilled in the art. Viroonchatapan et al. used thermosensitive dextran-magnetite magnetoliposomes in their in vitro experiments (Viroonchatapan et al, *Pharm. Res.* 1995; 12:1176-83), while Arcos et al. described a new type of biphasic magnetic glass-ceramic mixed with sol-gel glass that has the capability to act as thermoseeds (Arcos et al., *J. Biomed. Mater. Res.* 2003; 65A:71-8).

The claimed brachytherapy seed or strand may also be used for local cancer therapy. In a preferred embodiment, oxygen, hemoglobin, synthetic hemoglobin-like substances, and drugs that enhance tissue oxygen perfusion are included in the biodegradable substrate. Iwashita described a polymer oxygen carrier in U.S. Pat. No. 4,412,989. Bonaventura described a polymeric hemoglobin carrier in U.S. Pat. No. 4,343,715, and Chang described a biodegradable polymer containing hemoglobin in U.S. Pat. No. 5,670,173. Kakizaki et al. reported on a lipidheme synthetic microspheric oxygen carrier that released oxygen in tissue in vivo (*Artif. Cells. Blood Substit. Immobil. Biotechnol.* 1994; 22:933-8). Bobofchak et al. recently published their work on a recombinant polymeric hemoglobin designated Hb Minotaur (*Am. J. Physiol. Heart. Circ. Physiol.* 2003; 285:H549-61). Substances that can increase oxygen tension in tissue, include but are not limited to oxygen, L-arginine, papaverine, pentoxifylline, nicotinamide, and nitric oxide and various vasodilators.

Diagnostic compounds can be magnetic (detectable by MRI), radioopaque (detectable by x-ray), fluorescent (detectable by fluorescent techniques) or ultrasound detectable. These materials are commerically available, as are the systems for detection and measurements.

Radiopaque marker **30** can be made of any substance that can be detected by conventional X-ray imaging techniques. See, e.g., *Fundamentals of Diagnostic Radiology,* 2d ed., William E. Brant and Clyde A. Helms (eds.), Lippincott, Williams and Wilkins, 1999; *Physical Principles of Medical Imaging,* 2d ed., Perry Jr. Sprawls, Medical Physic Publishing, 1995; *Elements of Modern X-ray Physics*, Jens Als-Nielsen and Des McMorrow, Wiley & Sons, 2001; *X-ray and Neutron Reflectivity: Principles and Applications*, J. Daillant et al., Springer-Verlag, 1999; *Methods of X-ray and Neutron Scattering in Polymer Science*, Ryoong-Joon J. Roe, Oxford University Press, 2000; and *Principles of Radiographic Imaging: An Art & A Science*, Richard R. Carlton, Delmar Publishers, 2000. Many such substances that can be used as marker **30** are known including, most notably, high atomic number (i.e., "high Z") elements or alloys or mixtures containing such elements. Examples of these include platinum, iridium, rhenium, gold, tantalum, bismuth alloys, indium alloys, solder or other alloys, tungsten and silver. Many currently used radiopaque markers that might be adapted for use in the seeds described herein include platinum/iridium markers from Draximage, Inc. and International Brachytherapy; gold rods from Bebig GmbH; gold/copper alloy markers from North American Scientific, palladium rods from Syncor; tungsten markers from Best Industries; silver rods from Nycomed Amersham; silver spheres from International Isotopes Inc. and Urocor; and silver wire from Implant Sciences Corp. Other radiopaque markers include polymers impregnated with various substances (see, e.g., U.S. Pat. Nos. 6,077,880; 6,077,880; and 5,746,998). Radiopaque polymers are described in European Patent Application 894,503 filed May 8, 1997; European Patent Application 1,016,423 filed Dec.29, 1999; and published PCT application WO 96/05872 filed Aug. 21, 1995. Those radiopaque polymers that are biodegradable are preferred in applications where it is desired to have the implant degrade over time in the implantation site.

Examples of radiopaque markers include platinum, iridium, rhenium, gold, tantalum, bismuth, indium, tungsten, silver, or a radiopaque polymer. Suitable radioisotopes include ^{125}I and ^{103}Pd.

Sometimes combinations of agents may provide enhanced results. For example, in preferred embodiment, a radiosen-

sitizing agent such as 5-FU, etanidazole, tirapazamine, or BUdR, can be used in combination with IUdR. Various combinations of substances are known to be more effective when used in combination than when used alone. See, e.g., Brem et al., *J. Neurosur.* 80:283-290, 1994; Ewend et al., *Cancer Res.* 56:5217-5223, 1996; Cardinale, *Radiation Oncol. Investig.* 6:63-70, 1998; Yapp et al., *Radiotherapy and Oncol.* 53:77-84, 1999; Yapp, *IJROBP* 39:497-504, 1997; Yuan et al., *Radiation Oncol. Investig.* 7:218-230, 1999; and Menei et al., *Cancer* 86:325-330, 1999.

In addition to the biodegradable radiopaque marker in the seeds/strands, microbubbles may also be incorporated to facilitate ultrasonic detection. Micrometer-sized bubbles are known to be extremely potent scatterers of diagnostic frequencies, as reported by Hilgenfeldt et al., in *Ultrasonics* 2000; 38:99-104. Microbubble manufacturing is outlined by Schutt in U.S. Pat. No. 6,280,704 B1 and Schneider in U.S. Pat. No. 6,485,705 B1. The biodegradable microbubble substrate may be disposed within the seed or strand or on any or all of the outer aspect of the invention.

II. Formation of Polymeric Seeds

Although described in this application with especial reference to the formation of polymeric strands, it is understood that the same or similar technology can be used to make strands of the inorganic materials referenced above.

In one embodiment, polylactic acid strands can be fabricated using methods including solvent evaporation, hot-melt microencapsulation and spray drying. Polyanhydrides made of bis-carboxyphenoxypropane and sebacic acid or poly (fumaric-co-sebacic) can be prepared by hot-melt microencapsulation. Polystyrene strands can be prepared by solvent evaporation. Hydrogel strands can be prepared by dripping a polymer solution, such as alginate, chitosan, alginate/polyethylenimine (PEI) and carboxymethyl cellulose (CMC), from a reservoir though microdroplet forming device into a stirred ionic bath, as disclosed in WO 93/21906.

One or more diagnostic, therapeutic or prophylactic compounds can be incorporated into the polymeric strands either before or after formation.

Solvent Evaporation

Methods for forming strands using solvent evaporation techniques are described in E. Mathiowitz et al., *J. Scanning Microscopy,* 4:329 (1990); L. R. Beck et al., *Fertil. Steril.,* 31:545 (1979); and S. Benita et al., *J. Pharm. Sci.,* 73:1721 (1984). The polymer is dissolved in a volatile organic solvent, such as methylene chloride. A substance to be incorporated is added to the solution, and the mixture is suspended in an aqueous solution that contains a surface active agent such as poly(vinyl alcohol). The resulting emulsion is stirred until most of the organic solvent evaporated, leaving solid seeds or strands. Seeds and strands with different sizes (1-1000 μm diameter) and morphologies can be obtained by this method. This method is useful for relatively stable polymers like polyesters and polystyrene. However, labile polymers, such as polyanhydrides, may degrade during the fabrication process due to the presence of water. For these polymers, some of the following methods performed in completely anhydrous organic solvents are more useful.

Hot Melt Microencapsulation

Seeds can be formed from polymers such as polyesters and polyanhydrides using hot melt methods as described in Mathiowitz et al., *Reactive Polymers,* 6:275 (1987). In this method, the use of polymers with molecular weights between 3-75,000 Daltons is preferred. In this method, the polymer first is melted and then mixed with the solid particles of a substance to be incorporated that have been sieved to less than 50 μm. The mixture is suspended in a non-miscible solvent (like silicon oil), and, with continuous stirring, heated to 5° C. above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting seeds are washed by decantation with petroleum ether to give a free-flowing powder. Seeds and strands with diameters between 1 and 1000 μm are obtained with this method.

Solvent Extraction

This technique is primarily designed for polyanhydrides and is described, for example, in WO 93/21906, published Nov. 11, 1993. In this method, the substance to be incorporated is dispersed or dissolved in a solution of the selected polymer in a volatile organic solvent like methylene chloride. This mixture is suspended by stirring in an organic oil, such as silicon oil, to form an emulsion. Seeds that range between 1-300 μm can be obtained by this procedure.

Spray-Drying

Methods for forming seeds using spray drying techniques are well known in the art. In this method, the polymer is dissolved in an organic solvent such as methylene chloride. A known amount of a substance to be incorporated is suspended (insoluble agent) or co-dissolved (soluble agent) in the polymer solution. The solution or the dispersion then is spray-dried. Seeds ranging between 1 and 10 μm are obtained. This method is useful for preparing seeds for imaging of the intestinal tract. Using the method, in addition to metal compounds, diagnostic imaging agents such as gases can be incorporated into the seeds.

Phase Inversion

Seeds can be formed from polymers using a phase inversion method wherein a polymer is dissolved in a good solvent, fine particles of a substance to be incorporated, such as a drug, are mixed or dissolved in the polymer solution, and the mixture is poured into a strong non-solvent for the polymer, to spontaneously produce, under favorable conditions, polymeric seeds, wherein the polymer is either coated on the particles or the particles are dispersed in the polymer. The method can be used to produce microparticles in a wide range of sizes, including, for example, about 100 nm to about 10 μm. Exemplary polymers which can be used include polyvinylphenol and polylactic acid. Substances which can be incorporated include, for example, imaging agents such as fluorescent dyes, or biologically active molecules such as proteins or nucleic acids.

Protein Microencapsulation

Protein seeds can be formed by phase separation in a non-solvent followed by solvent removal as described in U.S. Pat. No. 5,271,961 to Mathiowitz et al. Proteins which can be used include prolamines such as zein. Additionally, mixtures of proteins or a mixture of proteins and a bioerodable material polymeric material such as a polylactide can be used. In one embodiment, a prolamine solution and a substance to be incorporated are contacted with a second liquid of limited miscibility with the prolamine solvent, and the mixture is agitated to form a dispersion. The prolamine solvent then is removed to produce stable prolamine seeds without crosslinking or heat denaturation. Other prolamines which can be used include gliadin, hordein and kafirin.

Low Temperature Casting of Seeds

Methods for very low temperature casting of controlled release seeds are described in U.S. Pat. No. 5,019,400 to Gombotz et al. In the method, a polymer is dissolved in a solvent together with a dissolved or dispersed substance to be incorporated, and the mixture is atomized into a vessel containing a liquid non-solvent at a temperature below the

freezing point of the polymer-substance solution, which freezes the polymer droplets. As the droplets and non-solvent for the polymer are warmed, the solvent in the droplets thaws and is extracted into the non-solvent, resulting in the hardening of the seeds.

Strands can also be made using many of the above-techniques using extrusion technology to elongate the seeds into strands.

Hydrogel Seeds

Seeds made of gel-type polymers, such as alginate, are produced through traditional ionic gelation techniques. The polymer first is dissolved in an aqueous solution, mixed with a substance to be incorporated, and then extruded through a microdroplet forming device, which in some instances employs a flow of nitrogen gas to break off the droplet. A slowly stirred ionic hardening bath is positioned below the extruding device to catch the forming microdroplets. The seeds are left to incubate in the bath for twenty to thirty minutes in order to allow sufficient time for gelation to occur. Particle size is controlled by using various size extruders or varying either the nitrogen gas or polymer solution flow rates.

Chitosan seeds can be prepared by dissolving the polymer in acidic solution and crosslinking it with tripolyphosphate. Carboxymethyl cellulose (CMC) seeds can be prepared by dissolving the polymer in acid solution and precipitating the microsphere with lead ions. Alginate/polyethylene imide (PEI) can be prepared in order to reduce the amount of carboxylic groups on the alginate microcapsule. The advantage of these systems is the ability to further modify their surface properties by the use of different chemistries. In the case of negatively charged polymers (e.g., alginate, CMC), positively charged ligands (e.g., polylysine, polyethyleneimine) of different molecular weights can be ionically attached.

Fluidized Bed

Particles, including seeds, can be formed and/or coated using fluidized bed techniques. One process is the Wurster air-suspension coating process for the coating of particles and seeds. The process consists of supporting the particles in a vertical column of heated air while the particles pass an atomizing nozzle that applies the coating material in the form of a spray. Enteric and film coating of seeds or strands by this process typically requires approximately 30 minutes. Suitable coating materials include, but are not limited to, cellulose acetate phthalate, ethylcellulose, hydroxypropyl methylcellylose, polyethylene glycol, and zein.

The Wurster apparatus provides controlled cyclic movement of the suspended particles by a rising stream of warm air, the humidity, temperature, and velocity of the air regulated. An air-suspended or fluidized bed of particles has a random movement. If seeds or strands move in and out of a coating zone in a random manner, the coating can be applied only at a slow rate. The Wurster apparatus, however, provides better drying and eventually a more uniform coating by imparting a controlled cyclic movement without or with less randomness. A support grid at the bottom of the vertical column typically includes a course screen, e.g., 10 mesh, and a fine screen, e.g., 200 mesh. The fine screen offers considerably more resistance to the air flow than the coarse screen; thus, the greater amount of air flows through the coarse screen. The air flowing through coarse screen lifts the seeds or strands upward in the column. As the velocity of the air stream is reduced due to diffusion of the stream and resistance of the seeds or strands, the upward movement of the seeds or strands ceases. Then the seeds or strands enter the region of a still lower velocity air stream above the fine screen, where they dry and gently settle. As the dried and partially coated seeds or strands approach the grid, they are again introduced into the higher-velocity air stream and the coarse screen, and enter into another cycle.

Below the grid support for the coarse screen, the coating fluid is dispersed by atomization under pressure. A compressed-air inlet is connected to the atomizing the solution or slurry of the coating material. The seeds or strands, which are suspended above the coarse screen, have little contact with each other, so the coating fluid is readily distributed onto the surface of the seeds or strands in the moving bed. As the cyclic movement of the seeds or strands continues, the seeds or strands are presented many times in many different positions to the atomized spray; therefore, a uniform coating is built up on the seeds or strands. Coating is controlled by the weight of the coated seeds or strands, formulation of the coating, temperature, time, and air velocity. Particle sizes can vary from about 50 μm to about 2 mm or greater.

IV. Method of Making Brachytherapy Strand for Implantation

One method of making a brachytherapy strand for implantation into a subject includes the steps of: (a) providing a non-metal biocompatible component and a therapeutically active diagnostic or prophylactic component (herein referred to as "therapeutically active component"), optimally further including an imaging agent or tracer, (b) physically associating the biocompatible component and the therapeutically active component to form a combination product; and (c) forming the combination product into a strand having a size and shape suitable for passing through the bore of a needle having an interior diameter of less than about 2.7 millimeters (10 gauge), less than about 1.4 millimeters (15 gauge), or less than about 0.84 millimeters (18 gauge), or less than about 0.56 millimeters (24 gauge).

Referring to the drawings there are illustrated various different embodiments of the brachytherapy strands. Although there is no lower limit as to how small any dimension of strand can be, in many applications, those that are not able to pass through bores smaller than 0.3 mm are preferred. For example, in many applications where it is desirable for the implanted brachytherapy strands to maintain their orientation in the tissue, the strand should be large enough to stay lodged at the site of implantation in the desired orientation for a relatively long period, larger strands are preferred. In some cases, the selection of materials for use in the strand will affect its size. For instance, in versions of the strand where the biocompatible component is a stainless steel or titanium capsule, the walls of the capsule may need to be greater than a certain minimum size in order to maintain the structural integrity of the strand. In addition, in some applications, the strand should also be large enough to carry a sufficient amount of the therapeutically active component to be therapeutically active (i.e., a therapeutically effective amount or an amount that exerts a desired medically beneficial effect). In order to facilitate the passage of the strand through the bore of a needle while preventing jamming of the brachytherapy implantation needle bore (e.g., caused by clumping of several strands), it is also preferred that the diameter of strand be just slightly less than the diameter of the bore of the needle (e.g., 0.5-5% less).

For use with the needles used in many conventional brachytherapy strand implantation devices, brachytherapy seeds shaped into a cylinder (or rod) having a diameter of between about 0.8 to 3 millimeters and a length of up to 40 millimeters are preferred. Because many conventional brachytherapy strand applicators make use of brachytherapy

implantation needles about 17 to 18 gauge in size, cylindrically shaped brachytherapy strands having a diameter of between about 0.8 and 1.1 mm and a length greater than the diameter (e.g., 2-10 mm) are preferred for use with such applicators. In particular, because many conventional brachytherapy strand applicators are designed to accept conventional radioactive brachytherapy strands that have a diameter of about 0.8 millimeters and a length of about 4.5 millimeters, brachytherapy strands of similar size are especially preferred.

Brachytherapy strands are not limited to those being cylindrical in shape, but rather can be any shape suitable for passing through the bore of a needle. For example, in many cases, the cross-sectional area of the strands can be cuboid, spheroid, ovoid, ellipsoid, irregularly shaped, etc. The ends of the strands can be rounded, squared, tapered, conical, convex, concave, scalloped, angular, or otherwise-shaped. The brachytherapy strands can be solid or have one or more cavities or pores (e.g., to increase the surface area of the strand exposed to the target tissue).

FIG. **1** is a schematic side view of a cylindrically shaped brachytherapy strand. FIG. **2** is a schematic side view of a hollow tube-shaped brachytherapy strand.

As one example, as illustrated in FIG. **2**, a brachytherapy strand **10** is shaped into a hollow tube **18** having a cylindrical cavity **20**. In preferred versions of strand **10**, cylindrical cavity **20** is sized to accept and envelop a standard-sized brachytherapy strand (e.g., one having a diameter of about 0.8 mm and a length of about 4.5 mm). For use, the strand **10** can be placed over the standard-sized brachytherapy strand, and introduced into the bore of a needle (sized to accept the enveloped strand) for implantation into a target tissue. The strand **10** shown in FIG. **2** can also be used alone without being placed over a standard-sized brachytherapy strand, e.g., to increase the surface area exposed in the site of implantation. Hollow tube **18** can have any wall thickness or length suitable for wholly or partially enveloping a standard-sized brachytherapy strand and passing through the bore of a needle. Preferably it has a wall thickness between about 0.01 and 0.1 mm and a length of between about 1 to 4.5 mm.

Referring again to FIGS. **1** and **2**, biocompatible component **12** can be composed of any material suitable for implantation in a target tissue in an animal subject (e.g., a mammal such as a human patient) that can be associated with therapeutically active component such that all or part of the therapeutically active component will be delivered to the target tissue when the brachytherapy strand **10** is introduced into the implantation site, as discussed above. For ease of use, ease of manufacture, and for therapeutic advantages, it is preferred that the biocompatible component **12** be biodegradable (i.e., made of a substance other than titanium or stainless steel).

A skilled artisan can select the particular composition of the component **12** that is most suited for a given application. For example, where the strand **10** is intended to be used to slowly deliver the therapeutically active component **14** when implanted in a target tissue, a biocompatible and biodegradable material made up of a chemical composition of a polymer known to degrade at a desired rate when placed under conditions similar to those encountered in the implantation site can be selected for use as component **12**. Various characteristics of such biodegradable components are described, e.g., in *Biomaterials Engineering and Devices: Human Applications: Fundamentals and Vascular and Carrier Applications*, Donald L. Wise et al. (eds), Humana Press, 2000; *Biomaterials Science: An Introduction to Materials in Medicine*, Buddy D. Ratner et al. (eds.), Academic Press, 1997; and *Biomaterials and Bioengineering Handbook*, Donald L. Wise, Marcel Dekker, 2000. For example, by selecting an appropriate material for use as the biocompatible component **12** of the brachytherapy strand **10**, the duration of release of the therapeutically active component **14** from strand **10** can be varied from less than about an hour to more than about several months (e.g., 10 min., 30 min., 1 h., 2 h., 3 h., 6 h., 12 h., 1 day, 2 days, 3 days, 1 week, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 1 year, 2 years, or 3 years). Biocompatible component **12** is not limited to being biodegradable. For example, in some cases, component **12** can also be made of a non-biodegradable material such as stainless steel or titanium. In this case, biocompatible component **12** can be coated or otherwise associated with therapeutically active component **14**, such that component **14** will be delivered to a target tissue into which strand **10** is implanted. For instance, component **12** might take the form of a porous stainless steel or titanium cylinder having a plurality of pores through its outer surface, such pores being filled with or otherwise in communication with the component **14** such that the component **14** can diffuse from the strand **10** into the environment surrounding the strand **10** (e.g., a target tissue).

These can be tested for suitability in a given application by conventional clinical testing. For example, a test composition can be fashioned into a brachytherapy strand and implanted in a laboratory animal in a selected target tissue. The effects of the implanted compositions on the animal can then be monitored over a period of time. Those that prove to be biocompatible (e.g., not causing an undesired response such as calcification or an allergic response) and have a desired rate of degradation and delivery of a therapeutically active component (if included in the test strand) can thus be identified.

As discussed above, the therapeutically active component **14** is a material that can be (a) implanted in a target tissue of an animal subject (e.g., a mammal such as a human patient) to exert an effect on the animal's physiology, and (b) associated with the biocompatible component **12** in the brachytherapy strand **10**. Myriad different substances can be used as the therapeutically active component **14**. See, e.g., Physician's Desk Reference, The Merck Index, and USP DI® 2000 published by U.S. Pharmacopeia. For example, the therapeutically active component **14** can include a small molecule drug (e.g., a non-peptide or non-nucleic acid-based molecule with a molecular weight generally less than 5 kDa) such as a chemical with known and-cancer properties. It can also include a biologic such as a polypeptide (e.g., an antibody or a cytokine) or nucleic acid (e.g., an expression vector). For example, where the strand **10** is intended to be used as a primary treatment for prostate cancer, the therapeutically active substance **14** can include an anti-neoplastic drug such as paclitaxel (taxol), cisplatin, or 5-fluorouracil; or a hormone such as leuprolide. As another example, where the strand **10** is intended to be used as an adjuvant to radiation treatment for prostate cancer, the therapeutically active substance **14** can include a radio-sensitizing agent such as tirapazamine, BUdR, IUdR, or etanidazole. Because brachytherapy strand **10** allows in situ drug delivery to a tissue, the therapeutically active substance **14** may include a drug that is usually considered too toxic to treat a given condition if given systemically, e.g., tirapazamine or camptothecin.

As indicated in the above description of the brachytherapy strand **10** shown in FIGS. **1** and **2**, the biocompatible component **12** is associated with the therapeutically active

component **14**. As used herein, when referring to the biocompatible component **12** and the therapeutically active component **14**, the phrase "associated with" means physically contacting. Thus, in the strand **10**, the association of the biocompatible component **12** with the therapeutically active component **14** can take many forms. For example, the biocompatible component **12** and the therapeutically active component **14** can be combined into a mixture as shown in FIGS. **1** and **2**. This mixture can have a uniform or non-uniform distribution of components **12** and **14**. The brachytherapy strand **10** shown in FIG. **1** is an example of a uniform mixture of components **12** and **14**. The brachytherapy strand **10** of this example can be made by simply mixing together the biocompatible component **12** and the therapeutically active component **14** to form a combination product and then forming the product into the desired size and shape, e.g., using a mold.

Although the brachytherapy strands shown in FIGS. **1** and **2** include mixtures of discrete particles dispersed through a matrix consisting of the therapeutically active component **14**, in other versions of brachytherapy strand **10**, components **12** and **14** are combined in a single particle or in a larger mass without discrete particles (e.g., a pellet the size and shape of brachytherapy strand **10**). For example, biocompatible component **12** and therapeutically active component **14** can be dissolved into a liquid and then dried or cured to form strands or a larger pellet made up of a homogeneous distribution of both components **12** and **14**. (see, e.g., Ramirez et al., *J. Microencapsulation* 16:105, 1999).

The skilled artisan can select the size according to the desired properties and particular properties of the microsphere constituents. In one variation of this, the strands are also made to include magnetic elements. The strands can then be molded or compressed together into the desired shape and size of brachytherapy strand **10**. The larger pellet can likewise be sculpted, extruded, molded or compressed into the desired shape and size of brachytherapy strand **10**. Alternatively, the liquid mixture of components **12** and **14** can be poured into a mold defining the shape and size of brachytherapy strand **10**, and then cured in the mold. Brachytherapy strands having components **12** and **14** combined in a single particle or in a larger mass (rather than discrete particles of each) are advantageous for delivering the therapeutically active component **14** into a target tissue over longer time periods.

In other embodiments of strand **10**, components **12** and **14** are not necessarily homogeneously mixed in the strand **10**. Rather they can be positioned in different areas of the strand **10**. For example, components **12** and **14** can be separately fashioned into discrete sections, strips, coils, tubes, etc. The discrete sections, strips, coils, tubes, etc. of the component **12** can then be combined (e.g., by molding together, adhering, structurally interlocking, etc.) with the discrete sections, strips, coils, tubes, etc. of the component **14** to form the strand **10**. In another embodiment, the strand **10** shown in FIG. **2** can be modified by filling the cylindrical cavity **20** with a hydrogel, including a therapeutically active substance, and capping off the ends of the hollow tube **18**.

These variations are more clearly understood by reference to the following figures. FIGS. **3**A-**3**I are strands with inert spacers **20**, interspersed for cutting (FIG. **3**A); with pop-up wings **22** to prevent migration or shifting after implanting (FIG. **3**B); with a radiopaque strip **30** running through it (FIG. **3**C); with cross-style stabilizers **32** (FIG. **3**D); with male **34** and female **36** ends to facilitate joining, e.g., in a ring (FIG. **3**E); with indentations **38** for cutting or breaking into smaller strands (FIG. **3**F); with a stabilizer, such as bumps **40** (FIG. **3**G); as braided strand **42** (FIG. **3**H); and strands knotted together **44** (FIG. **3**I). FIGS. **4**A and **4**B are a strand **50** with radioactive seeds **52** interspersed (perspective view, FIG. **4**A; cross-sectional view, FIG. **4**B).

The foregoing combination products (i.e., at least one biocompatible component mixed with at least one therapeutically active component) can be used in the brachytherapy strands by forming them into a size and shape suitable for passing through the bore of a needle such as one in a conventional brachytherapy strand implantation device. Referring now to FIGS. **3**A-I, in others, a brachytherapy strand **10** includes a biocompatible component **12** associated with a therapeutically active component **14**, and a radiopaque marker **30** (not shown except in FIG. **3**C) attached to the biocompatible component **12** and/or the therapeutically active component **14**. Radiopaque marker **30** allows for the position of brachytherapy strand **10** to be determined using standard X-ray imaging techniques (e.g., fluoroscopy) after strand **10** has been implanted in a target tissue. Proper positioning of strand **10** and spacing of a plurality of brachytherapy strands in a given target tissue is important for ensuring that the therapeutically active component **14** is delivered adequately to the site of the disease in the target tissue.

As indicated above, radiopaque marker **30** is attached to strand **10** via the biocompatible component **12** and/or the therapeutically active component **14**. The exact manner in which radiopaque marker **30** is attached to strand **10** can is not critical so long as (a) the strand **10** can be passed through the bore of a brachytherapy implantation needle and (b) the attachment allows the position of strand **10** to be readily detected by X-ray imaging. A description of some different examples of how marker **30** can be associated with strand is presented in FIGS. **3**A-F. In the embodiment shown in FIG. **3**A, the radiopaque marker **30** in the form of a ribbon, filament, strip, thread, or wire is placed in the center and along the length of cylindrical strand **10**. In FIG. **3**B, the radiopaque marker **30** takes the form of two end caps placed at both ends of cylindrical strand **10**. In the embodiment illustrated in FIG. **3**C, the radiopaque marker **30** is a coil made of a radiopaque substance running through the length of cylindrical strand **10** as shown. In FIG. **3**D, the radiopaque marker **30** takes the form of two heads or pellets placed at two locations along cylindrical strand **10**. In the embodiment shown in FIG. **3**E, the radiopaque marker **30** takes the form of two bands or rings placed at two locations along the outer surface of cylindrical strand **10**. In the strand **10** shown in FIG. **3**F, the radiopaque marker **30** takes the form of a mesh formed into cylindrical shape. In the strand **10** shown in FIG. **3**G, the radiopaque marker **30** is dispersed throughout the strand in a stippled pattern.

FIGS. **4**A and **4**B are a strand with radioactive seeds interspersed (perspective view, FIG. **4**A; cross-sectional view, FIG. **4**B).

A particularly preferred embodiment of a brachytherapy strand having a radiopaque marker is one in which the radiopaque marker is a polymer. In one version of this embodiment, radiopaque polymers are combined with a biocompatible component and a therapeutically active component to form a brachytherapy strand that can be visualized by X-ray imaging. Alternatively, the radiopaque polymer can serve as the biocompatible component. For example, strands made of a radiopaque polymer are co-mingled with strands containing a biocompatible component and strands containing (e.g., encapsulating) a therapeutically active component (or strands containing both a biocompatible

component and a therapeutically active component). The co-mingled strands are then molded into a radiopaque brachytherapy strand. As another example, the radiopaque polymer, the biocompatible component, and the therapeutically active component can be mixed together into a liquid, and the liquid can be cured to form a solid pellet that can be sculpted, molded, compressed, or otherwise made into the size and shape of a brachytherapy strand. An advantage of preparing a radiopaque brachytherapy strand in this manner is that, after implantation, the entire strand can be visualized by X-ray imaging rather than only a portion of a strand (e.g., as occurs with strands utilizing conventional markers).

FIGS. **5**A-**5**D are perspective views of strands after introduction into breast adjacent to lumpectomy site (larger circle) below the nipple (smaller circle) (FIG. **5**A); strands conforming to shape of breast with patient now upright, lumpectomy site is shown as larger black circle, nipple as smaller circle (FIG. **5**B); strand deployed as a coil (FIG. **5**C); and strands deployed as rings around lumpectomy site (FIG. **5**D).

FIG. **6** is a magnified depletion of microfabricated polyimide hairs. By covering the brachytherapy seed or strand with these polyimide hairs, the problem of seed migration can be effectively overcome. Seed migration involves movement of seeds from their implanted location, usually during the interval immediately following seed placement. Two precipitating causes are felt to be a recoil effect in tissue as it springs back from deformation caused by the seed introducer needle, and suction along the exit path caused by the needle as it is withdrawn after depositing seeds. Several papers in the literature have addressed this issue (see for example, Tapen et al., *IJROBP* 1998; 42:1063-7, Merrick et al., *IJROBP* 2000; 46:215-20, Poggi et al., *IJROBP* 2003; 56:1248-51).

One method of overcoming this problem is to secure seeds together in a coaxial array within suture strand material such that seeds are kept at a fixed distance from one another. Another approach is to attach each seed to an interlocking peg (see Grimm U.S. Pat. No. 6,450,939B1), again to create a fixed arrangement. However, these systems are fixed by definition, and can present logistical problems when one is working with irregularly shaped targets, or targets that are split by intervening tissue that one wishes to avoid. Furthermore, the strands themselves can migrate, skewing the dosimetry for an entire row of seeds.

Prior art brachytherapy seeds have not satisfactorily addressed the issue of limiting individual seed movement along the needle track. Giem et al have succeeded in producing microfabricated polyimide hairs, and showed that their artificial hairs produce capillary and van der Waals forces which impart particular adhesive properties (Giem et al., *Nature Materials* 2003; 2:461-3). These polyimide hairs have been constructed based on the structure of gecko foot-hairs (setae) which have been shown to have astounding adhesive properties. The polyimide hairs have diameters from 0.2-4 micrometers, heights from 0.15-2 micrometers, and periodicity from 0.4-4.5 micrometers.

The hairs were made as long as possible, and have sufficient flexibility so that individual tips can attach to uneven surfaces all at the same time, and do not break, curl or tangle. Care was taken not to make the hairs too thin, lest they fall down, or too dense, lest they bunch. In order to overcome the problems associated with seed and strand migration, setae technology is used to cover or coat the biodegradable seeds and strands with hairs that impart comparable adhesive potential.

When seeds and strands are implanted into tissues, those tissues am unevenly distributed around the implanted material. The compliant setal structure permits conformance to the shape of a contacting structure, increasing the magnitude of the attractive van der Waals forces as the tiny hairs act together. Similarly, as the seeds and strands are pushed out of their introducing needle, they are dragged over the tissue, which increases setal adhesion. Larger setae create larger sticking forces from larger setal contact areas.

Finally, the tissue is moist since it is living tissue, and setae have improved adhesive properties when they are moist. All of these factors make biodegradable setae (protrusions) an ideal solution to seed/strand migration [see FIG. **6**].

FIGS. **7**A and **7**B illustrate brachytherapy strand geometries such that the brachytherapy strand has one or more conduits running along the length of the strand. These conduits can be pre-filled or fillable, and are useful in the delivery of therapeutic and diagnostic agents to the surrounding implanted tissue. The agents need not be biodegradable themselves, but should be fluid enough to pass through the conduits. Optionally, there can be a pore, series of pores, or network of pores and conduits along the strands through which the agents flow out into the surrounding tissue. In another embodiment, there can be a portal that can be accessed with a needle or other introducer instrument through the skin, or the portal can protrude out of the body via a percutaneous connection to the conduit system. The radioactive material in the strand, if present, can be separated from the conduit system by intervening non-radioactive material. Sundback et al described a similar system in *Biomaterials* 2003; 24:819-30 wherein the conduits were used to contour nerve growth.

The therapeutically active agent **14** in strand **10** including the sealed container **40** can be any of those agents described above. Preferably, however, agent **14** is selected to provide an enhanced effect when used in combination with the radioisotope to treat a particular diseased tissue, as discussed above.

The radioisotope can be any substance that emits electromagnetic radiation (e.g., gamma-rays or X-rays), beta-particles or alpha-particles and is suitable for use in brachytherapy strand **10**. Examples of such substances include those that decay principally by electron capture followed by X-ray emission such as palladium-103 and iodine-125; isotopes that decay by the emission of beta-particles such as gold-198, gold-199, yttrium-90, and phosphorus-32; isotopes that decay with the emission of both beta-particles and gamma-rays such as iridium-192; and isotopes that decay with the emission of alpha-particles such as americium-241. Also useful is gadolinium-157, e.g., for use in boron-neutron capture therapy, and californium-252, rhenium-188, samarium-153, indium-111, ytterbium-169, and holmium-166. For the treatment of prostate cancer, palladium-103 and iodine-125 are preferred as these have been the subject of much clinical investigation for the treatment of the disease. The amount of radioactivity of radioisotope can vary widely. For example, when using palladium-103 or iodine-125, an exemplary amount to treat prostate cancer is respectively about 1.5 mCi and 0.33 mCi per strand, if about 50-150 strands are used at the time of implantation. In other applications the radioactivity per strand can range from about 0.01 mCi to about 100 mCi.

In one embodiment, the radioisotope can be mixed with and then configured into strands, or it can be encapsulated by the biocompatible component to form strands. The radioactive strands can be molded or otherwise sized and shaped

into a brachytherapy strand suitable for implantation via a brachytherapy implantation device. In one version of this embodiment, the biocompatible component is biodegradable such that the radioisotope contained by this component is gradually released from the strand. Alternatively, the biocompatible component and radioisotope can be mixed together and configured as an amorphous pellet having the size and shape of a brachytherapy strand suitable for implantation via a brachytherapy implantation device.

In a preferred embodiment in which the brachytherapy strand contains radionuclide, the strand is coated with a non-radioactive biodegradable coating which degrades at a rate slower than that which allows the radioactivity to leach out, so that radioactivity is not released —i.e., the radioactivity has already fully decayed.

FIGS. **8**A, **8**B and **9** depict the addition of polymeric anchoring structures to brachytherapy strands. Biodegradable seeds may also be equipped with a similar system, but on a smaller scale. As noted above, migration can be problematic. Built-in ridges, bumps, and related structures can ameliorate this problem to some extent, but will not completely eliminate it.

Biodegradable shape memory polymeric (Lendlein et al., *Science* 2002; 296:1673-6) structures which deploy to their pre-trained shape after implantation in order to maintain the seeds in the desired location may also be used. Such structures can ideally include grapple-shaped anchors at the ends of a brachytherapy strand [see FIG. **8**A]. These hooks deploy following introduction of the strand into the target tissue. Similar structures can be interspersed the length of the strand, oriented such that the strand becomes locked m position [see FIG. **8**B]. The same concept can be used to brace or center the strands within a target tissue in instances where that tissue contains a cavity, defect or other irregular space that might otherwise kink, bend, or offset the strand [see FIG. **9**].

These may be bristle-life, ring-shaped, or alternative shapes depending upon the choice made by those skilled in the art. Similarly, they can space apart adjacent strands, thereby avoiding clumping or bunching. Optionally, these structures may or may not contain the therapeutic or diagnostic agents. The shape memory structures are activated by heat from the implanted tissue, or are pre-heated prior to implantation to trigger their deployment.

As with the shape memory polymer above, electroactive polymers (EAPs) or polymer hybrids may be used for stabilization, spacing, or related purposes. Hybrid substrates can include biodegradable polymer/semiconductor composites. These components expand, contract, bend, or otherwise change shape or size displacement upon exposure to an applied voltage. These types of changes can be induced with very low voltage input which can be achieved without harming the host tissue. Pelrine described this style device in U.S. Pat. No. 6,545,384 B1, as did Kornbluh in U.S. Pat. No. 6,586,859B2.

Electronic EAPs can include ferroelectric polymers, dielectric polymers, electrorestrictive graft elastomers, electro-viscoelastic elastomers, liquid crystal elastomer materials, or other related polymers or organic substances. Ionic EAPs can include ionic polymer gels, ionomeric polymer-metal composites, conductive polymers, carbon nanotubes, or other related polymers or organic substances (see for example Bar-Cohen et al., ed., *Electroactive Polymers and Rapid Prototyping: Materials Research Society Symposium Proceedings*, Materials Research, 2002; *Applications of Electroactive Polymers*, (Stienen, ed.), Kluwer Academic Publishers, 1993; Zhang et al., *Nature* 2002; 419:284-7). Scheibel et al. described the use of biomolecular templates as conducting nanowires in *PNAS* 2003; 100,4527-32. In this instance, amyloid formed by prions was the biomolecular substance used to create the nanowires. Various physicochemical factors, such as light, temperature, and pH can be applied to the "smart polymers" or other substrates to achieve similar configuration modification.

Spacers can be made of a biocompatible material that can be used to join two brachytherapy seeds. See, e.g., U.S. Pat. No. 6,010,446. The biocompatible material can be either biodegradable or non-biodegradable. For example, spacers can be made of catgut or a like material. Spacers designed for use with conventional radioactive brachytherapy seeds can be used in chain. For example, Ethicon, Inc. (Cincinnati, Ohio) manufactures the PG 910 non-sterile autoclavable spacer for Indigo (Cincinnati, Ohio) that is sold in conjunction with an Express Seed Cartridge. In addition, Medical Device Technologies, Inc. (Gainesville, Fla.) distributes a pre-sterilized 5.5 mm long absorbable pre-cut spacer that is made of collagen (Lock®, model number 1514b). Materials for use as the spacer are also manufactured by Surgical Specialties Corp. (Reading Pa.). Where the spacer is made of a relatively flexible material, the chain can be relatively flaccid.

Where the brachytherapy strand or linker is formed of an elastic polymer such as elastin-like peptides, polyhydroxyalkanoates (PHAs) or poly(glycol-sebacate), or some protein, the strand or chain is becomes high deformable. Such deformability is particularly advantageous when implanting tissues or organs whose shape may become distorted by normal body motion, such as the breasts or viscera. Where the chain is endowed with the flexibility of an elastic polymer or similar substance, the chain may be considered to be variably flexible rather than rigid or flaccid. The precise degree of flexibility will depend upon the composition of the carrier matrix. Those skilled in the art will be accustomed to selecting the ration of component substances in the carrier matrix such that the desired degree of flexibility is achieved. This flexibility, rather than being simply linear or curved, can be in any direction. In some embodiments, the chain may be spiral-shaped or otherwise twisted, springy, or bent to conform to the desired shape. In other embodiments, the chain can form a lattice or mesh whereby one or mom chains can be interconnected through linking mechanisms, knots, ties, welds, fusions, or other methods known to those skilled in the art. In yet another embodiment, the chain may be introduced into the target tissue in one shape, only to be purposefully or intentionally modified or altered to another advantageous shape thereafter.

Spacers can be connected to seed by any means known. For example, spacer can be connected to seed by direct attachment such as by gluing, crimping, or melting. Spacers can be attached to any portion of the seed. For rod or cylinder-shaped seeds, to facilitate implantation, it is generally preferred that spacers are attached to the ends of the seeds so that the ends are adjacent to one another when the chain is inserted into the barrel of a brachytherapy implantation needle. In one preferred embodiment, the spacer and seed are indistinguishable linked such that no seams, welds, or joints are visible. In another embodiment, the spacer may be of a different color, texture, diameter, hardness, or shape for easy identification and demarcation. This can include a translucent coloration. In still another embodiment, the spacer may be indented or otherwise marked somewhere along its length as an indication of where the seed/spacer chain can be safely cut, spliced, broken, or otherwise sepa-

rated without exposing active therapeutic substances such as radionuclides that are contained within the seed.

In another embodiment, spacers may be omitted in favor of a continuous array of seeds that may form a chain or strand. This is especially advantageous when implanting an organ such as the breast, where discrete seeds are not necessarily required to achieve the desired dispersement of radioactivity and/or other therapeutic substances. The continuous seed array without interruption by spacer is especially preferred when the implanted strands contain an elastic polymer or other flexible carrier for use in a mobile organ or tissue. In yet another embodiment, spacers may be located at varying distances from one another, separated by different lengths of continuous seed arrays, depending upon the clinical circumstances. Depending upon the discretion of the clinician, more than one continuous seed and/or spacer array may be implanted along a given row to achieve the desired effect in tissue.

Where spacers are used, spacer and seed, however, need not be physically attached to each other. Rather they can also be associated with each other by placing each with within the lumen of a tube. The tube can be used to load a brachytherapy seed implantation device with a plurality of spacers and seeds in any sequence. For example, the brachytherapy seed implantation device can be loaded with one (or 2, 3, 4, 5, or more) spacer being interposed between every two seeds. Similarly, the brachytherapy seed implantation device can be loaded with one (or 2, 3, 4, 5, or more) seed being interposed between every two spacers.

VI. Methods of Implantation

The brachytherapy strands are implanted into a target tissue within a subject (e.g., a human patient or a non-human animal) by adapting known methods for implanting conventional radioactive brachytherapy seeds into a tissue. For example, the brachytherapy strands can be implanted using one or more implantation needles; Henschke, Scott, or Mick applicators; or a Royal Marsden gold grain gun (H. J. Hodt et al., *British J. Radiology*, pp. 419-421, 1952). A number of suitable implantation devices are described in, e.g., U.S. Pat. Nos. 2,269,963; 4,402,308; 5,860,909; and 6,007,474.

In many applications to treat a given target tissue with a therapeutic agent, it is desirable (or even ideal) to fully saturate the target tissue with the therapeutic agent, while avoiding under- or over-dosing the target tissue. This can be achieved by implanting the brachytherapy strands into a target tissue using a brachytherapy implantation device so that a precise number of strands can be implanted in precise locations within the target tissue. By previously calculating the rate of diffusion of the therapeutically active substance under experimental conditions (e.g., using tissue from animal models), an appropriate dosage can be delivered to the target tissue. Because use of brachytherapy implantation devices allows the brachytherapy strands to be implanted in any number of different desired locations and/or patterns in a tissue, this method is advantageous over methods where a drug or drug impregnated matrix is simply placed on the surface of a tissue or manually inserted into a surgically dissected tissue.

In one preferred method of use, the strands are introduced into the target organ through a puncture site with a brachytherapy needle, obviating the need for an incision, suturing of a catheter, tracheostomy, or prolonged insertion of an often uncomfortable or painful metallic or plastic foreign body into the patient. In the case of the base of tongue, the hairpin needles are withdrawn following loading of the strands, thereby limiting the degree of swelling that occurs and possibly sparing the patient the need for a tracheostomy. In the case of a lumpectomy for removal of a breast cancer, the strands can be placed in the same fashion as temporary iridium-192 or iodine-125 metallic seed strands, but without the sutures and buttons anchoring the catheters or needles and strands to the skin for retrieval later.

I claim:

1. A strand for administration of a therapeutic agent to a subject in need thereof comprising (a) a therapeutically effective amount of a therapeutic agent; (b) a biocompatible component comprising a polymer; (c) a radio-opaque material, wherein the radio-opaque material is encapsulated in the biocompatible component; and (d) a polymeric coating, wherein the therapeutic agent is a small molecule, wherein the polymeric coating covers the strand and wherein radiopaque material allows for the position of the strand to be determined following administration wherein the strand is non-radioactive and does not contain a radioisotope.

2. The strand of claim **1**, wherein the radio-opaque material is imageable.

3. The-strand of claim **1**, wherein the radio-opaque material comprises a high Z element.

4. The strand of claim **1**, wherein the device/strand is an implant.

5. The strand of claim **1** in the form of a rod or cylinder.

6. The strand of claim **5**, wherein the rod comprises one or more pores or cavities.

7. The strand of claim **1**, having a diameter between 0.5 and 3 mm and a length of 40 mm.

8. The strand of claim **7**, wherein the strand has a diameter of 2 mm.

9. The strand of claim **5**, wherein the rod has open ends.

10. A strand for administration of a therapeutic agent to a subject in need thereof comprising (a) a therapeutically effective amount of a therapeutic agent; (b) a biocompatible component comprising a non-biodegradable polymer; (c) a radio-opaque material, wherein the radio-opaque material is encapsulated in the biocompatible component; and (d) a polymeric coating, wherein the therapeutic agent is a small molecule and wherein the polymeric coating covers the strand, wherein the strand is non-radioactive and does not contain a radioisotope.

11. The strand of claim **1**, having a diameter between 0.8 and 3 mm and a length of 40 mm.

12. The strand of claim **1**, having a length of up to 50 cm.

13. The strand of claim **1**, wherein the strand is in the form of a rod or cylinder, and the therapeutic agent is a hormone.

14. The strand of claim **13**, having a diameter between 0.5 and 3 mm and a length of 40 mm.

15. The strand of claim **13**, wherein the therapeutic agent is not an anti-neoplastic agent.

16. A strand for administration of a therapeutic agent to a subject in need thereof comprising (a) a therapeutically effective amount of a therapeutic agent; (b) a biocompatible component comprising a polymer; (c) a radio-opaque material, wherein the radio-opaque material is encapsulated in the biocompatible component; and (d) a polymeric coating, wherein the polymeric coating covers the strand and wherein radiopaque material allows for the position of the strand to be determined following administration wherein the strand is non-radioactive and does not contain a radioisotope.

17. The strand of claim **16**, wherein the strand is in the form of a rod or cylinder, and the therapeutic agent is a hormone.

18. The strand of claim **17**, having a diameter between 0.5 and 3 mm and a length of 40 mm.

19. The strand of claim **17**, wherein the therapeutic agent is not an anti-neoplastic agent.

* * * * *

EXHIBIT D

US009636401B2

(12) **United States Patent**
Kaplan

(10) **Patent No.: US 9,636,401 B2**
(45) **Date of Patent: *May 2, 2017**

(54) **FLEXIBLE AND/OR ELASTIC BRACHYTHERAPY SEED OR STRAND**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 84 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/473,159**

(22) Filed: **Aug. 29, 2014**

(65) **Prior Publication Data**

US 2015/0010470 A1 Jan. 8, 2015

Related U.S. Application Data

(63) Continuation of application No. 13/916,916, filed on Jun. 13, 2013, now Pat. No. 8,821,835, which is a continuation of application No. 12/823,700, filed on Jun. 25, 2010, now Pat. No. 8,470,294, which is a continuation of application No. 10/665,793, filed on Sep. 19, 2003, now Pat. No. 7,776,310, which is a continuation-in-part of application No. 09/861,326, filed on May 18, 2001, now Pat. No. 6,746,661, said application No. 10/665,793 is a continuation-in-part of application No. 09/861,196, filed on May 18, 2001, now Pat. No. 6,514,193.

(60) Provisional application No. 60/412,050, filed on Sep. 19, 2002, provisional application No. 60/249,128, filed on Nov. 16, 2000.

(51) **Int. Cl.**

A61K 49/04	(2006.01)
A61K 41/00	(2006.01)
A61K 47/48	(2006.01)
A61K 51/12	(2006.01)
A61N 5/10	(2006.01)
A61K 49/00	(2006.01)
A61B 5/06	(2006.01)
A61L 31/14	(2006.01)
A61L 31/10	(2006.01)
A61L 31/16	(2006.01)
A61L 31/18	(2006.01)
A61B 90/00	(2016.01)

(52) **U.S. Cl.**

CPC ***A61K 41/0038*** (2013.01); ***A61B 5/064*** (2013.01); ***A61B 90/39*** (2016.02); ***A61K 47/48992*** (2013.01); ***A61K 49/00*** (2013.01); ***A61K 49/0409*** (2013.01); ***A61K 51/1282*** (2013.01); ***A61L 31/10*** (2013.01); ***A61L 31/146*** (2013.01); ***A61L 31/148*** (2013.01); ***A61L 31/16*** (2013.01); ***A61L 31/18*** (2013.01); ***A61N 5/1007*** (2013.01); ***A61N 5/1027*** (2013.01); *A61B 2090/3966* (2016.02); *A61L 2300/44* (2013.01); *A61N 2005/1023* (2013.01); *A61N 2005/1024* (2013.01)

(58) **Field of Classification Search**

CPC A61K 49/00; A61K 49/08; A61K 51/00; A61K 51/12

USPC 424/1.11, 1.25, 1.29, 9.4; 623/1.1, 1.34, 623/1.38

See application file for complete search history.

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(57) **ABSTRACT**

A flexible or elastic brachytherapy strand that includes an imaging marker and/or a therapeutic, diagnostic or prophylactic agent such as a drug in a biocompatible carrier that can be delivered to a subject upon implantation into the subject through the bore of a brachytherapy implantation needle has been developed. Strands can be formed as chains or continuous arrays of seeds up to 50 centimeters or more, with or without spacer material, flaccid, rigid, or flexible.

25 Claims, 6 Drawing Sheets

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FIG. 1

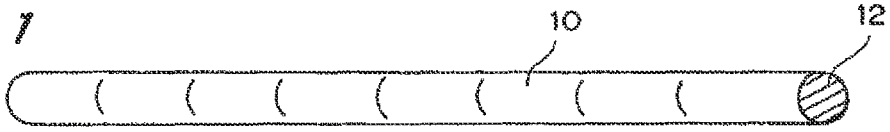


FIG. 2

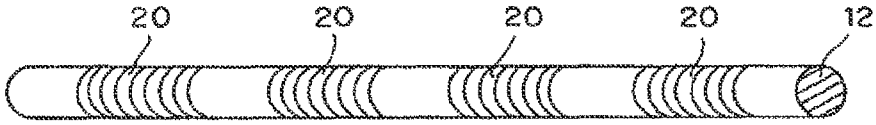


FIG. 3A

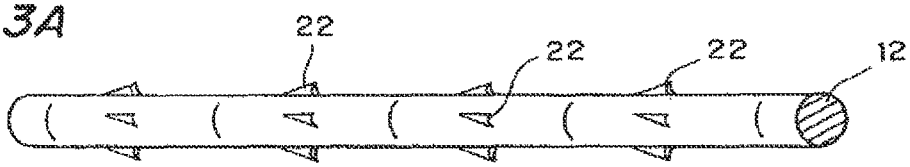


FIG. 3B

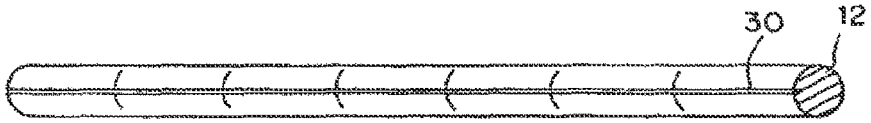


FIG. 3C

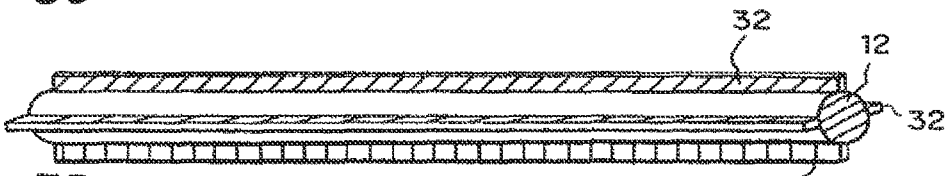


FIG. 3D

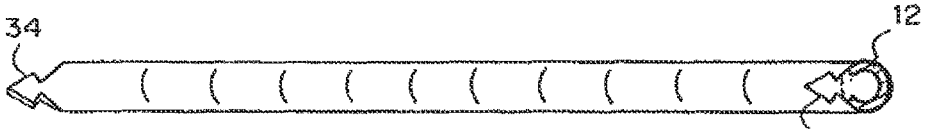
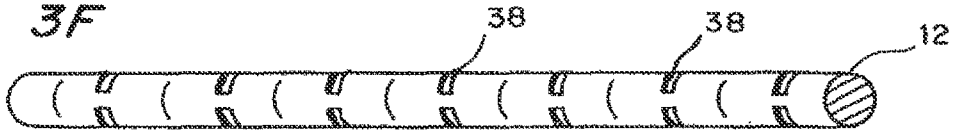


FIG. 3E

FIG. 3F



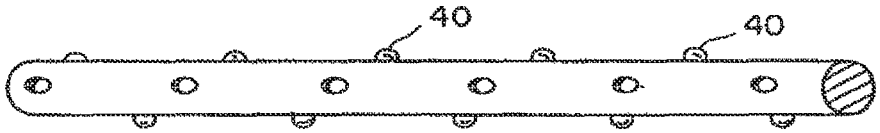


FIG. 3G

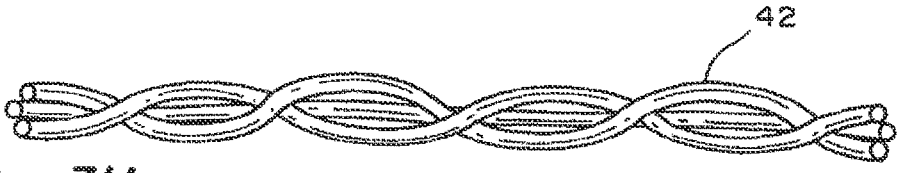


FIG. 3H

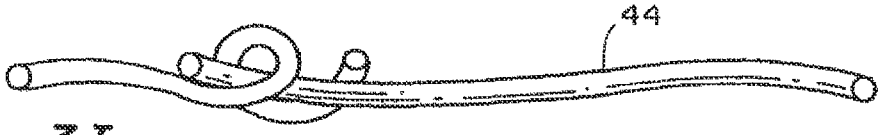


FIG. 3I

FIG. 4A

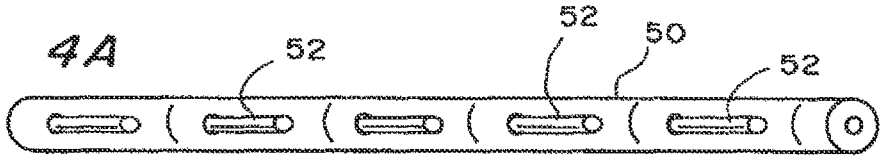


FIG. 4B

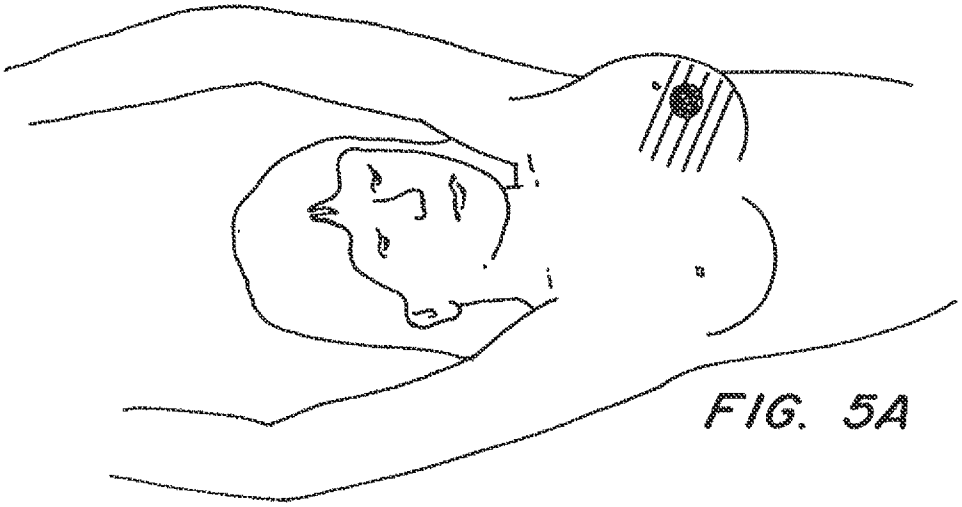


FIG. 5A

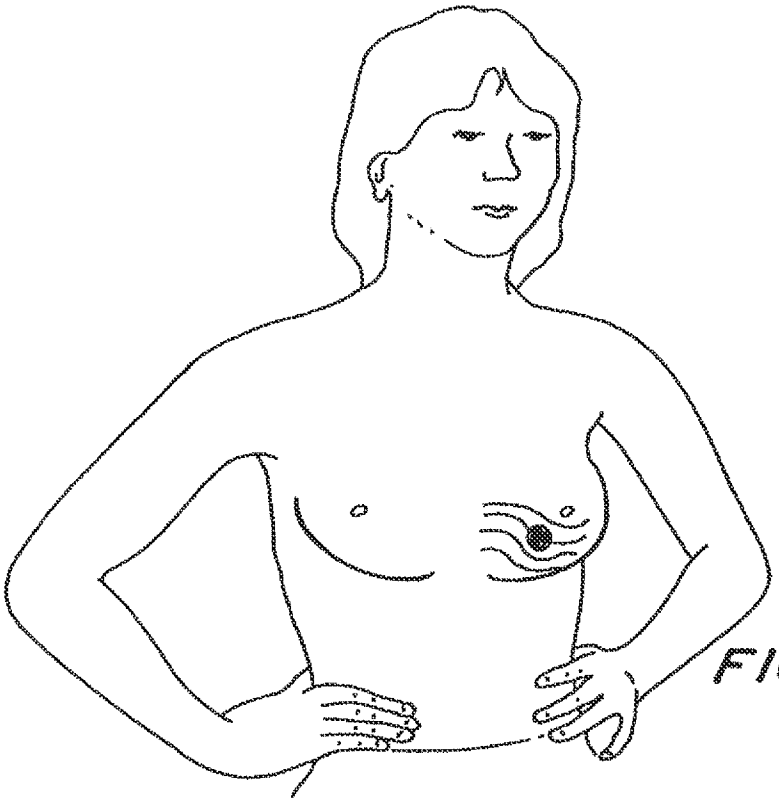


FIG. 5B

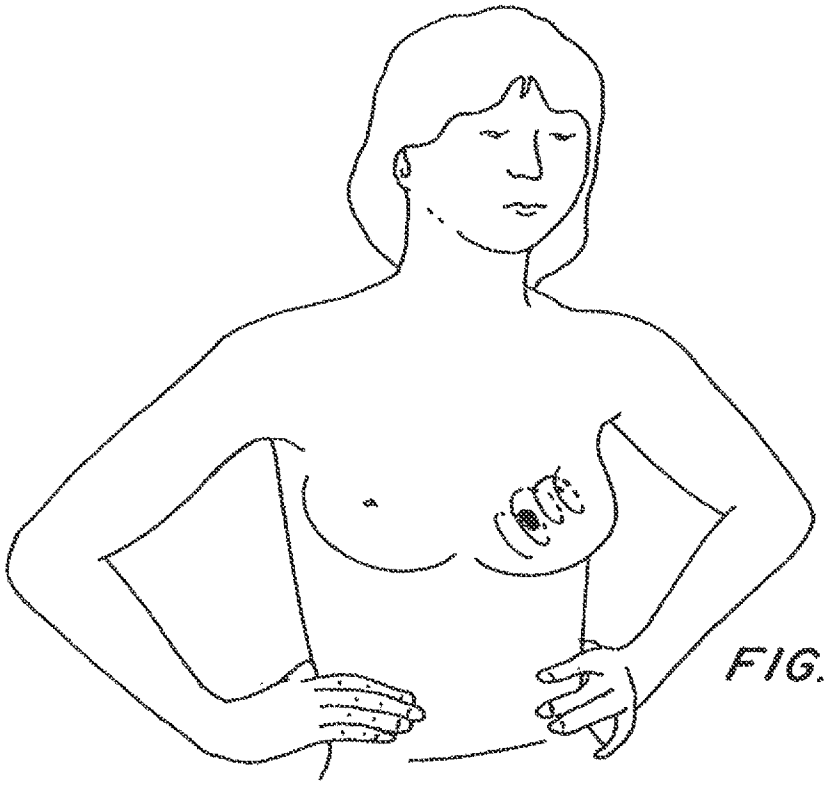


FIG. 5C

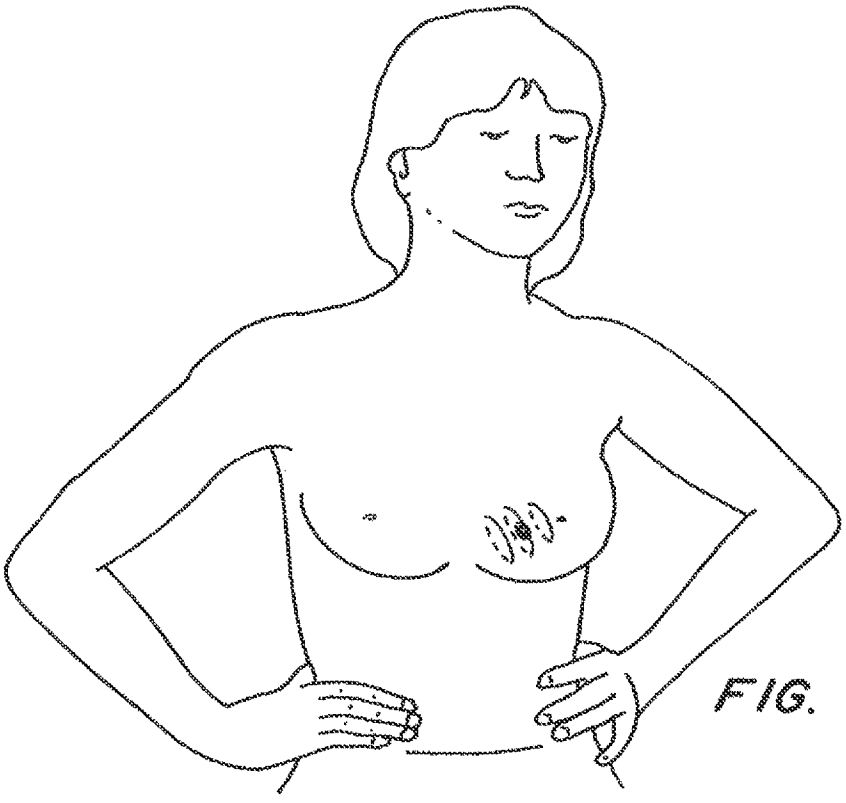
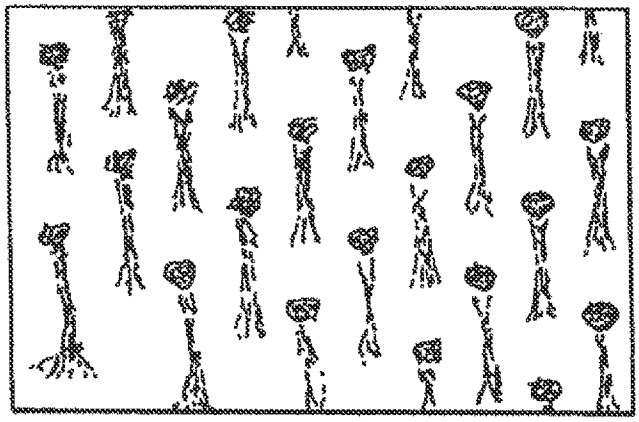


FIG. 5D

FIG. 6



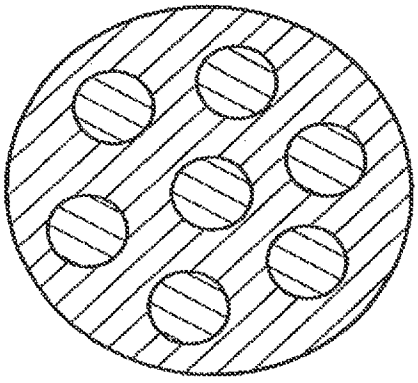


FIG. 7A

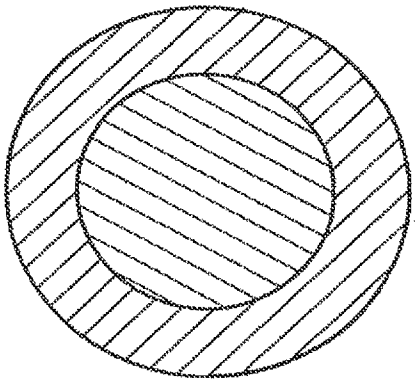


FIG. 7B

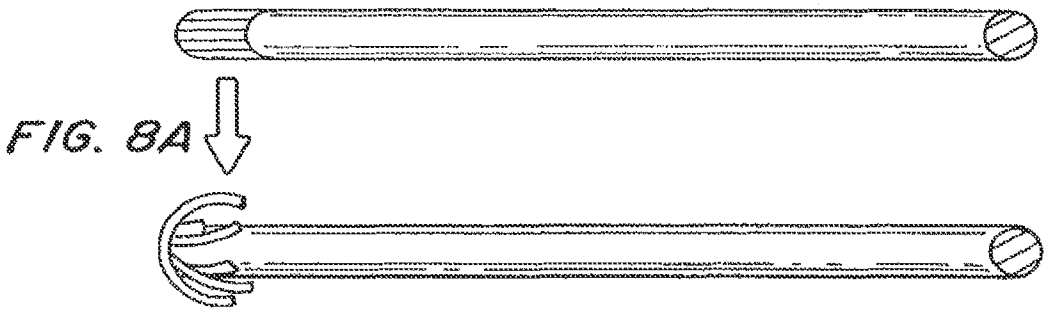


FIG. 8A

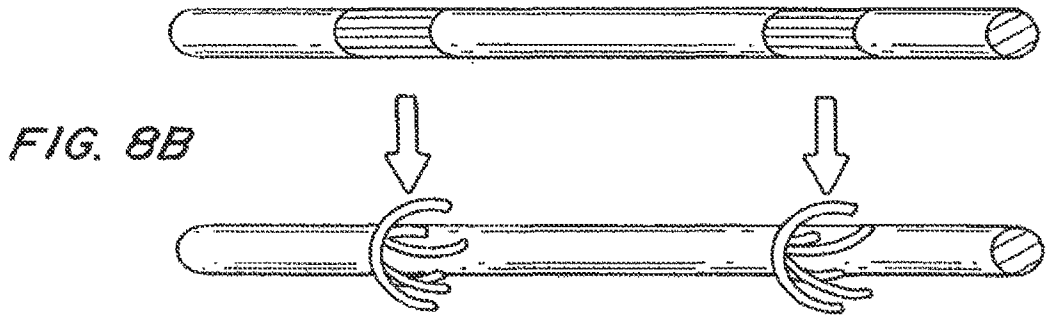


FIG. 8B

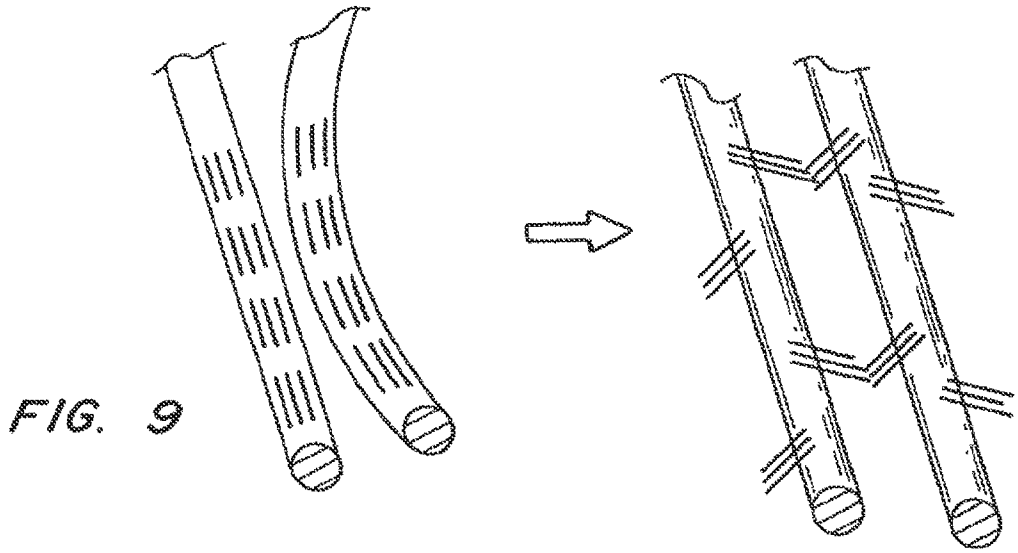


FIG. 9

FLEXIBLE AND/OR ELASTIC BRACHYTHERAPY SEED OR STRAND

The present application is a continuation of U.S. application Ser. No. 13/916,916, filed Jun. 13, 2013, entitled "Flexible and/or Elastic Brachytherapy Seed or Strand", by Edward J. Kaplan, which is a continuation of U.S. application Ser. No. 12/823,700, filed Jun. 25, 2010, now U.S. Pat. No. 8,470,294, issued Jun. 25, 2013, which is a continuation of U.S. application Ser. No. 10/665,793, filed Sep. 19, 2003, now U.S. Pat. No. 7,776,310, issued Aug. 17, 2010, which claims priority to and benefit of U.S. Provisional Application No. 60/412,050, filed Sep. 19, 2002, and is a continuation-in-part of U.S. Ser. No. 09/861,326 filed May 18, 2001, now U.S. Pat. No. 6,746,661, issued Jun. 8, 2004, which claims priority to and benefit of U.S. Provisional Application No. 60/249,128 filed Nov. 16, 2000, and U.S. application Ser. No. 10/665,793, filed Sep. 19, 2003, now U.S. Pat. No. 7,776,310, issued Aug. 17, 2010 is also a continuation-in-part of U.S. Ser. No. 09/861,196 filed May 18, 2001, now U.S. Pat. No. 6,514,193, issued Feb. 4, 2003, which claims priority to and benefit of U.S. provisional application 60/249,128 filed Nov. 16, 2000.

BACKGROUND OF THE INVENTION

This application relates to imagable implantable brachytherapy devices, and methods of use thereof.

Radioactive seed therapy, commonly referred to as brachytherapy, is an established technique for treating various medical conditions, most notably prostate cancer. In a typical application of brachytherapy for treating prostate cancer, about 50-150 small seeds containing a radioisotope that emits a relatively short-acting type of radiation are surgically implanted in the diseased tissue. Because the seeds are localized near the diseased tissue, the radiation they emit is thereby concentrated on the cancerous cells and not on distantly located healthy tissue. In this respect, brachytherapy is advantageous over conventional external beam radiation.

A number of devices have been employed to implant radioactive seeds into tissues. See, e.g., U.S. Pat. No. 2,269,963 to Wappler; U.S. Pat. No. 4,402,308 to Scott; U.S. Pat. No. 5,860,909 to Mick; and U.S. Pat. No. 6,007,474 to Rydell. In a typical protocol for treating prostate cancer, an implantation device having a specialized needle is inserted through the skin between the rectum and scrotum into the prostate to deliver radioactive seeds to the prostate. The needle can be repositioned or a new needle used for other sites in the prostate where seeds are to be implanted. Typically, 20-40 needles are used to deliver between about 50-150 seeds per prostate. A rectal ultrasound probe is used to track the position of the needles. Once the end of a given needle is positioned in a desired location, a seed is forced down the bore of the needle so that it becomes lodged at that location.

As the seeds are implanted in the prostate as desired, the needles are removed from the patient. Over the ensuing several months the radiation emitted from the seeds kills the cancerous cells. Surgical removal of the seeds is usually not necessary because the type of radioisotope generally used decays over the several month period so that very little radiation is emitted from the seeds after this time Currently marketed radioactive seeds take the form of a capsule encapsulating a radioisotope. See, e.g., Symmetra® I-125 (Bebig, GmbH, Germany); IoGold™ I-125 and IoGold™ Pd-103 (North American Scienific, Inc., Chatsworth, Calif.);

Best® I-125 and Best® Pd-103 (Best Industries, Springfield, Va.); Brachyseed® I-125 (Draximage, Inc., Canada); Intersource® Pd-103 (International Brachytherapy, Belgium); Oncoseed® I-125 (Nycomed Amersham, UK); STM 1250 I-125 (Sourcetech Medical, Carol Stream, Ill.); Pharmaseed® I-125 (Syncor, Woodland Hills, Calif.); Prostaseed™ I-125 (Urocor, Oklahoma City, Okla.); and I-plant® I-125 (Implant Sciences Corporation, Wakefield, Mass.). The capsule of these seeds is made of a biocompatible substance such as titanium or stainless steel, and is tightly sealed to prevent leaching of the radioisotope. The capsule is sized to fit down the bore of one of the needles used in the implantation device. Since most such needles are about 18 gauge, the capsule typically has a diameter of about 0.8 mm and a length of about 4.5 mm.

The two radioisotopes most commonly used in prostate brachytherapy seeds are iodine (I-125) and palladium (Pd-103). Both emit low energy irradiation and have half-life characteristics ideal for treating tumors. For example, I-125 seeds decay at a rate of 50% every 60 days, so that at typical starting doses their radioactivity is almost exhausted after ten months. Pd-**103** seeds decay even more quickly, losing half their energy every 17 days so that they are nearly inert after only 3 months.

Radioactive brachytherapy seeds may also contain other components. For example, to assist in tracking their proper placement using standard X-ray imaging techniques, seeds may contain a radiopaque marker. Markers are typically made of high atomic number (i.e. "high Z") elements or alloys or mixtures containing such elements. Examples of these include platinum, iridium, rhenium, gold, tantalum, lead, bismuth alloys, indium alloys, solder or other alloys with low melting points, tungsten, and silver. Many radiopaque markers are currently being marketed. Examples include platinum/iridium markers (Draximage, Inc. and International Brachytherapy), gold rods (Bebig GmbH), gold/copper alloy markers (North American Scientific), palladium rods (Syncor), tungsten markers (Best Industries), silver rods (Nycomed Amersham), silver spheres (International Isotopes Inc. and Urocor), and silver wire (Implant Sciences Corp.). Other radiopaque markers include polymers impregnated with various substances (see, e.g., U.S. Pat. No. 6,077,880).

A number of different U.S. patents disclose technology relating to brachytherapy. For example, U.S. Pat. No. 3,351,049 to Lawrence discloses the use of a low-energy X-ray-emitting interstitial implant as a brachytherapy source. In addition, U.S. Pat. No. 4,323,055 to Kubiatowicz; U.S. Pat. No. 4,702,228 to Russell; U.S. Pat. No. 4,891,165 to Suthanthiran U.S. Pat. No. 5,405,309 to Carden; U.S. Pat. No. 5,713,828 to Coniglione; U.S. Pat. No. 5,997,463 to Cutrer; U.S. Pat. No. 6,066,083 to Slater; and U.S. Pat. No. 6,074,337 to Tucker disclose technologies relating to brachytherapy devices.

The seeds have also been utilized to treat other types of cancers, such as pancreas, liver, lung and brain. For technical reasons, other organ systems or tissues are not amenable to this type of permanent seed implantation. These include hollow viscera such as the urinary bladder, mobile/muscular viscera such as the base of tongue, and tissues where a cavity or tumor bed has been created as a result of resection, as in the breast. In hollow viscera, loose seeds cannot be reliably spaced out owing to a dearth of tissue and the associated risk of losing the seeds into the lumen or cavity of the organ. Likewise in mobile/muscular and irregularly shaped viscera such as the base of tongue, loose seeds cannot be spaced reliably, and strands of permanent seeds

like those described in U.S. Pat. No. 4,754,745 to Horowitz or U.S. Pat. No. 5,322,499 to Liprie are still too inflexible to be used because of the metallic seeds that are embedded within them. Similarly, the wire coils described in U.S. Pat. No. 6,436,026 to Sioshansi, although flexible, are not meant to be implanted permanently and require a means of afterloading and removal.

The situation in breast cancer is similar to that of a hollow organ, whereby loose seeds are difficult to space properly, and may fall into the resection cavity, thus spoiling the dosimetry plan. Despite U.S. Patent application No. 20020087078 by Cox which describes the insertion of a radioactive seed into a breast with cancer, the seed is placed inside the actual breast cancer and is removed along with the tumor at the time of the cancer surgery. Therefore, in this instance, the radioactive seed is not meant to serve a therapeutic purpose. Breast tissue is also similar to the base of tongue or other mobile organs since the breast may be very generous and supple, conforming to forces of gravity or pressure. In fact, for these reasons, metallic seeds are not currently used for permanent therapeutic implantation into a breast.

In each of the above circumstances where use of permanent seeds is not desirable, temporary implants are generally used. This is accomplished via placement of afterloading devices such as the Henschke applicator for cervix cancer, hairpin needles for the base of tongue, and silastic catheters for breast cancer. Once the respective applicators have been placed, radioactive sources are loaded and remain indwelling for a prescribed finite period, usually hours to days. The sources and afterloading devices are then completely removed.

Disadvantages of these temporary systems are that patients often must stay in the hospital for the cadre time that low dose rate sources are indwelling, or between radiotherapy fractions or sessions if high dose rate sources are used. In the case of afterloading catheters, the catheters are sutured in place for several days, causing acute pain, swelling, and possible infection or scarring. In the case of base of tongue implants, patients frequently require temporary tracheostomies to keep their airway open while the hairpin needles remain in place. In one new temporary high dose rate system by Proxima Therapeutics®, surgical placement of a balloon catheter is performed on the breast. The device has a catheter leading from the balloon in the tumor bed to the skin to provide ingress and egress for the temporary brachytherapy source. The balloon is deflated at the conclusion of several days of brachytherapy sessions, and is pulled out of the breast by hand.

It is an object of the present invention to provide biodegradable strands or other structures that are flexible and permanently implantable.

It is another object of the present invention to provide biodegradable strands or other structures that are flexible and implantable.

It is still another object of the present invention to provide non polymeric biodegradable implantable seeds and a means for readily imaging implanted seeds.

It is also an object of the present invention to provide brachytherapy seeds and strands which can be used for ether purposes, for example, drug delivery.

SUMMARY OF THE INVENTION

A brachytherapy strand that is elastic and/or flexible and preferably biodegradable has been developed. A drug or other therapeutically active substance or diagnostic can be included in the strand in addition to, or as an alternative to, a radioisotope. The rate of release in the implantation site can be controlled by controlling the rate of degradation and/or release at the implantation site. In the preferred embodiment, the strands also contain a radioopaque material or other means for external imaging. The flexible material may be polymeric or inorganic material. Strands can be formed as chains or continuous arrays of seeds up to 50 centimeters or more, with or without spacer material, flaccid, rigid, or flexible.

Like conventional radioactive brachytherapy seeds, the strands can be precisely implanted in many different target tissues without the need for invasive surgery. In the preferred embodiment, the strands are implanted into the subject through the bore of a brachytherapy implantation needle or catheter. The therapeutically active substance included within a strand can be delivered in a controlled fashion over a relatively long period of time (e.g., weeks, months, or longer periods). Since concentrations of the therapeutically active substance will be greater at the implantation sue (e.g., the diseased tissue), any potential deleterious effect of the therapeutically active substance on healthy tissue located away from the implantation site will be reduced.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic side view of a cylindrically shaped brachytherapy strand.

FIG. **2** is a schematic side view of a hollow tube-shaped brachytherapy strand.

FIGS. **3**A-**3**I are strands with inert spacers, interspersed for cutting (FIG. **3**A); with pop-up wings to prevent migration or shifting after implanting (FIG. **3**B); with a radiopaque strip running through it (FIG. **3**C); with cross-style stabilizers (FIG. **3**D); with male and female ends to facilitate joining, e.g., in a ring (FIG. **3**E); with indentations for cutting or breaking into smaller strands (FIG. **3**F); with a stabilizer, such as bumps (FIG. **3**G); a braided strand (FIG. **3**H); and strands knotted together (FIG. **3**I).

FIGS. **4**A and **4**B are a strand with radioactive seeds interspersed (perspective view, FIG. **4**A; cross-sectional view, FIG. **4**B).

FIGS. **5**A-**5**D are perspective views of strands after introduction into breast adjacent to lumpectomy site (larger circle) below the nipple (smaller circle) (FIG. **5**A); strands conforming to shape of breast with patient now upright, lumpectomy site is shown as larger black circle, nipple as smaller circle (FIG. **5**B); strand deployed as a coil (FIG. **5**C); and strands deployed as rings around lumpectomy site (FIG. **5**D).

FIG. **6** is a depiction of microfabricated polyimide hairs used as a coating for the brachytherapy seed or strand to impart adhesive properties.

FIGS. **7**A and **7**B are transverse cross-section views of a brachytherapy strand with multiple internal conduits (FIG. **7**A) or a single conduit (FIG. **7**B).

FIGS. **8**A and **8**B are depictions of a brachytherapy strand equipped with shape memory polymeric anchoring structures at the ends of the strand (FIG. **8**A) and interspersed along the length of the strand (FIG. **8**B), before and after deployment.

FIG. **9** is a depiction of a brachytherapy strand equipped with shape memory polymeric anchors positioned to brace or center the strands within irregularly shaped tissues.

DETAILED DESCRIPTION OF THE INVENTION

An elastic and/or flexible, and preferably biodegradable, brachytherapy seed or strand of seeds, has been developed.

As used herein "elastic" refers to a material which has the ability to recover from relatively large deformations, or withstand them, or which can be elongated to multiple times its original length, without breaking. In one preferred embodiment, the brachytherapy strand includes a biocompatible component, a therapeutically active component that includes a non-radioactive drug, and in a more preferred embodiment, a radiopaque marker. The biocompatible component is physically associated with a therapeutically active component and in contact with the marker. In a second embodiment, the brachytherapy strand includes a non-metal biocompatible component, a therapeutically active component comprising a radioisotope, and a radiopaque or other diagnostic marker, the biocompatible component being (a) physically associated with a therapeutically active component and (b) in contact with the diagnostic marker, wherein the brachytherapy strand has a size and shape suitable for passing through the bore of a needle typically having an interior diameter of less than about 2.7 millimeters (10 gauge). In another embodiment, the biocompatible component is biodegradable.

Depending on the particular application, the brachytherapy strands offer other advantages. Among these, for example, compared to conventional systemic administration (e.g., oral or intravenous delivery) of therapeutically active substances, the brachytherapy strands can provide higher and more consistent concentrations of a therapeutically active substance to a target tissue. They can also eliminate the need for repeated injections as well as circumvent delivery problems such as where a target tissue lacks an intact vascular supply (e.g., a target tissue whose blood flow may be compromised) or is otherwise sequestered from the blood supply (e.g., via the blood-brain barrier of the central nervous system). In some embodiments of the strands that do not contain a radioisotope (e.g., those having only the therapeutically active substance and biodegradable component), after the therapeutically active substance is completely released and the biodegradable component is fully decomposed, no foreign device will remain at the implantation site.

I. Brachytherapy Strands.

Brachytherapy strands typically have a size and shape suitable for passing through the bore of a needle having an interior diameter of less than about 2.7 millimeters (10 gauge), less than about 1.4 millimeters (15 gauge), less than about 0.84 millimeters (18 gauge), or less than about 0.56 millimeters (24 gauge). In one version, the strand is shaped into a cylinder having a diameter of between about 0.5 to 3 millimeters and a length of 20, 30, 40 centimeters or more.

A. Materials for Making the Brachytherapy Seeds.

Any appropriate biocompatible material can be used to form the brachytherapy seeds. Preferred materials include polymeric materials which are approved by the Food and Drug Administration for plantation.

In the preferred embodiment, the seeds are formed of a biodegradable material. Examples of suitable materials include synthetic polymers such as polyhydroxyacids (polylactic acid, polyglycolic-lactic acid), polyanhydrides (poly (bis(p-carboxyphenoxy) propane anhydride, poly(bis(p-carboxy) methane anhydride), copolymer of polycarboxyphenoxypropane and sebacic acid); polyorthoesters; polyhydroxyalkanoates (polyhydroxybutyric acid); and poly (isobtaylcyanoacrylate). Other examples include open cell polylactic acid; co-polymers of a fatty acid dimer and sebacic acid; poly(carboxyphenoxy) hexane; poly-1,4-phenylene dipropionic acid; polyisoplithalic acid; polydodecanedioic acid; poly(glycol-sebacate) (PGS); or other polymers described below. See, e.g., Biomaterials Engineering and Devices: Human Applications: Fundamentals and Vascular and Carrier Applications, Donald L. Wise et al. (eds), Humana Press, 2000; *Biomaterials Science: An Introduction to Materials in Medicine*, Buddy D. Ratner et al. (eds.), Academic Press, 1997; and *Biomaterials and Bioengineering Handbook*, Donald L. Wise, Marcel Dekker, 2000.

These polymers can be obtained from sources such as Sigma Chemical Co., St, Louis, Mo.; Polysciences, Warrenton, Pa.; Aldrich, Milwaukee, Wis.; Fluke, Ronkonkoma, N.Y.; and BioRad, Richmond, Calif., or can be synthesized from monomers obtained from these or other suppliers using standard techniques.

In addition to synthetic polymers, natural polymers may also be used. In the preferred embodiment, the natural polymers are biodegyadable. For example, tissue such as connective tissue from the walls of blood vessels or extracellular matrix may be used as a biodegradable carrier for delivery of radiation or another therapeutic substance. See, for example, U.S. Pat. No. 5,429,634 to Narcisco. Tissue may be autologous, heterologous, engineered, or otherwise modified so long as it is biocompatible with the target tissue. A patient may donate his own tissue to serve as a carrier for the therapeutic substance and/or radionuclide. Other tissues or natural polymers may serve as the degradable carrier matrices. For example, polysaccharides such as starch and dextran, proteins such as collagen, fibrin (Perka, et al., Tissue Eng. 7:359-361 (2001) and Senderoff, et al., J. Parenteral Sci. 45:2-6 (1991)), and albumin (see, for example, U.S. Pat. No. 5,707,644 to Ilum), elastin-like peptides, lipids, and combinations thereof. These materials can be derived from any of the sources known to those skilled in the art, including the patient's own tissues or blood.

Seeds or strands can also be made from synthetic or natural biocompatible non-polymeric and/or inorganic materials, which are preferably biodegradable. See for example, WO 99/53898 describing bioabsorbable porous silicon seeds and WO 00/50349 describing biodegradable ceramic fibers from silica sols. Other examples of non-polymeric and/or organic materials include: U.S. Pat. No. 5,640,705 to Koruga describing radiation-containing fullerene molecules; WO 02/34959A2 by Yeda Research and Development Co, Ltd. describing inorganic fullerene-like nanoparticles or structures; EP 1205437A1 to Osawa describing nano-size particulate graphite and multi-layer fullerene; U.S. Pat. No. 5,766,618 to Laurencin describing a polymeric-hydroxyapatite bone composite; GB 235140A to Asako Matsushima describing a ceramic composite such as hydroxyapatite for sustained release; and U.S. Pat. No. 5,762,950 to Antti Yli-Urpo disclosing a calcium phosphate, e.g. hydroxyapatite, bioactive ceramic for timed release.

In the case of radioactive seeds, it can be left to the clinician to select from any number of biodegradable carder matrices which contain the radionuclide, so king as the degradation characteristics of the carrier substance are consistent with the desired absorption profile. This is because the carrier matrix itself will be sequestered from the surrounding target tissue along with the radionuclide until the radionuclide has decayed to an insignificant activity. At that time or afterwards, the biodegradable layer overlying the radioactive matrix will be eroded away, thus beginning is similar process for the now non-radioactive or nearly spent radioactive carder.

Strands may also be made of non-biodegradable materials, especially the radioopaque strand materials currently used to form beads for treatment of prostate cancer, although

this is not as preferred as the biodegradable materials. As described above, the capsule (and as described herein, the strand) of these seeds is made of a biocompatible substance such as titanium or stainless steel, which is tightly sealed to prevent leaching of the radioisotope.

B. Radioactive Tracers

Optionally, brachytherapy seed or strand can be imparted with a means of tracing the radioactive contents should those contents be released inadvertently. Unforeseen problems associated with leakage of radioactive material, whether it be into the surrounding tissues in a patient, in a pathology lab, in a nuclear medicine lab, or in the operating room have been recently discovered as they relate to polymer seeds. The seed/strand should contain a means of tracing their contents should those contents be released inadvertently. This mechanism can rely on inclusion of fluorescent, luminescent, colored, pigmented or other approaches for tagging, detecting, or otherwise identifying the seed/strand contents either visually or with instrument assistance.

Fluorescence can be imparted using the appropriate polymer or other biodegradable substance, such as described by Sung in U.S. Pat. No. 4,885,254, Bryan in U.S. Pat. No. 6,416,960 B1, Barbera-Guillem in U.S. Pat. No. 6,548,171 B1, or Greiner in U.S. Patent Application No. 2003/0010508A1.

Luminescence can be imparted using the appropriate polymer or other biodegradable substance, such as described by Towns in WO01/49768 A2, Sakakibara in EP 1 311 138 A1, Bryan in U.S. Pat. No. 6,436,682B1, Hancock in U.S. Patent Application No. 2003/0134959A1, or Wood in U.S. Pat. No. 6,552,179B1. Bioluminescence materials are described in U.S. Pat. No. 5,670,356. In addition, chemiluminescent and electro luminescent substances might be utilized, as we as other types of luminescent substances as would be known to one skilled in the art.

Quantum dots may also be loaded into the seeds and utilized to locate spilled substances from ruptured seeds/strands, like those described in U.S. Patent Application No. 2003/0129311A1 or Dobson in WO 95/13891 (see also Jaiswal et al., *Nature Biotechnology* 2003; 21:47-51, and Quantum Dot Corporation's Qdot™ biotin conjugate).

Dyed biodegradable polymeric material may be used, as described by Burkhard in EP 1 093 824 A2. Other dyes can be used as indicated. Ultraviolet light can be utilized to detect a therapeutic agent like radioactive substances or drugs using a format described by Koshihara in U.S. Pat. No. 6,456,636 B1, or by Nakashima in WO 00/53659. Infrared dyes may be used, as described by Paulus in U.S. Pat. No. 5,426,143.

Those skilled in the art will be familiar with labeling, doping, or tagging the contents of the seeds/strands with agents that can be identified without modification, or pro-agents that can be identified by the addition of an activating substance or other means, such as labeled antibodies and the like.

C. Therapeutic and Diagnostic Agents

Polymers can be used to form, or to coat, drug delivery devices such as strands or strands containing any of a wide range of therapeutic and diagnostic agents. Any of a wide range of therapeutic, diagnostic and prophylactic materials can be incorporated into the strands, including organic compounds, inorganic compounds, proteins, polysaccharides, and nucleic acids, such as DNA, using standard techniques.

The non-radioactive drug can take the form of stimulating and growth factors; gene vectors; viral vectors; anti-angiogenesis agents; cytostatic, cytotoxic, and cytocidal agents; transforming agents; apoptosis-inducing agents; radiosensitizers; radioprotectants; hormones; enzymes; antibiotics; antiviral agents; mitogens; cytokines; anti-inflammatory agents; immunotoxins; antibodies; or antigens. For example, the non-radioactive therapeutic can be an anti-neoplastic agent such as paclitaxel, 5-fluorouracil, or cisplatin. It can also be a radiosensitizing agent such as 5-fluorouracil, etanidazole, tirapazamine, bromodeoxyuridine (BUdR) and iododeoxyuridine (IUdR).

Many different therapeutically active substances have been associated with biocompatible materials for use in drug delivery systems apart from brachytherapy strands. These include, for example, adriamycin (Moritera et al., *Invest. Ophthal. Vis. Sci.* 33:3125-30, 1992); bupivicaine (Park et al., *J. Controlled Release* 52:179-189, 1998); camptothecin (Weingart et al., *Int. J. Cancer* 62:1-5, 1995); carboplatin (Chen et al., *Drug Delivery* 4:301-11, 1997); carmustine (Brem et al., *J. Neurosurg* 74:441-6, 1991; and U.S. Pat. Nos. 4,789,724 and 5,179,189); cefazolin (Park et al., *J. Controlled Rel.* 52:179-189, 1998); cisplatin (Yapp et al., *IJROBP* 39:497-504, 1997); cortisone (Tamargo et al., *J. Neurooncol.* 9:131-8, 1990); cyclosporine (Sanchez et al., *Drug Delivery* 2:21-8, 1995); daunorubicin (Dash et al., *J. Pharmacol. Tox. Meth.* 40:1-12, 1999); dexamethasone (Reinhard et al., *J Contr. Rel.* 16:331-340, 1991); dopamine (During et al., *Ann. Neurol.* 25:351-6, 1989); etanidazole (Yapp et al., *Radiotherapy Oncol.* 53:77-84, 1999); 5-fluorouracil (Menei et al., *Cancer* 86:325-30, 1999); fluconazole (Miyamoto et al., *Curr. Eye Res.* 16:930-5, 1997); 4-hydroxycyclophosphamide (Judy et al., *J. Neurosurg,* 82:481-6, 1995); ganciclovir (Kunou et al., *J. Controlled Rel.* 37:143-150, 1995); gentamicin (Laurentin et al., *J. Orthopaed. Res.* 11:256-62, 1993); heparin (Tamargo et al., *J. Neurooncol.* 9:131-8, 1990); interleukin-12 (Kuriakose et al., *Head & Neck* 22:57-63, 2000); naproxen (Conforti et al., *J. Pharm. Pharmacol.* 48:468-73, 1996); nerve growth factor (Camerata et al., *Neurosurgery* 30:313-19, 1992); retroviral vector producer cells to transfer a cytotoxic gene product (Beer et al., *Adv. Drug Deliver. Rev.* 27:59-66, 1997); taxol (Park et al., *J. Controlled Rel.* 52:179-189, 1998; and Harper, E et al., *Clin. Cancer Res.,* 5:4242-4248, 1999); tetanus toxoid (Alonso et al., *Vaccine* 12:299-306, 1994); tetracaine hydrochloride (Ramirez et al., *Microencap.* 16:105-15, 1999); tirapazamine (Yuan et al., *Radiation Oncol. Investig.* 7:218-30, 1999); thyrotropin-releasing hormone (Kubek et al., *Brain Res.* 809:189-97, 1998); and vaccines (Chattaraj et al., *J. Controlled Rel.* 58:223-32, 1999). Other therapeutically active substances that can be combined with a biocompatible component include: anesthetics, angiogenesis inhibitors (e.g., Lau D. H. et al., *Cancer Biother. Radiopharm.* 14:31-6, 1999), antibiotics (e.g., Bahk J. Y. et al., *J. Urol.* 163:1560-4, 2000; and Miyamoto H. et al., *Current Eye Research* 16:930-5, 1997), antibodies (e.g., Gomez S. M. et al., *Biotechnol. Prog.* 15:238-44, 1999), anticoagulants (e.g., Tamargo R. J. et al., J. Neurooncol. 9:131-138, 1990), antigens (e.g., Machluf M. et al., J. Pharm. Sci. 89:1550-57, 2000), anti-inflammatory agents (e.g., Reinhard C. S. et al., J. Controlled Release 16:131-40, 1991; and Tamargo R. J. et al., J. Neurosurg. 74; 956-61 1991), antivirals, apoptosis-inhibiting agents (e.g., Macias D. et al., Anat. Embryol. (Berl) 193:533-41, 1996), cytokines (e.g., Edelman E. R. et al., Biomaterials 12:619-26, 1991), cytotoxic agents (e.g., Brem H. et al., J. Neurosurg, 80:283-90, 1994; Brem H. et al. J. Neurosurg. 80:283-90, 1994; Brem H. et al., Lancet 345:1008-12, 1995; Ewend M. G. et al., Cancer Res. 56:5217-23, 1996; Fung L. K. et al., Cancer Res. 58:672-85, 1998; Grossman S. et al., J.

Neurosurg, 76:640-47, 1992; Kong Q. et al., J. Surgical Oncology 69:76-82, 1998; Shikani A. H. et al., Laryngoscope 110:907-17, 2000; Straw R. C. et al., J. Orthop. Res. 12:871-7, 1994; Tamargo R. J. et al., Cancer Research 53:329-33, 1993; Valtonen S. et al., Neurosurgery 41:44-9, 1997; Walter K. A. et al., Cancer Research 54:2207-12, 1994; Yapp D. T. T. et al, IJROBP 39:497-504, 1997; Yapp D. T. T. et al., Anti-Cancer Drugs 9:791-796, 1998; Yapp D. T. T. et al., IJROBP 42:413-20, 1998; and Yoshida M. et al., Biomaterials 10:16-22, 1989), enzymes (e.g., Park T. G. et al., J. Control Release 55:181-91 1998), gene vectors (e.g., Hao T. et al, J. Control Release 69:249-59, 2000; and Maheshwari A. et al., Mol. Ther. 2:121-30, 2000), hormones (e.g., Rosa G. D. et al., J. Control Release 69:283-95, 2000), immunosuppressants (e.g., Sanchez A. et al., Drug Delivery 2:21-8, 1995), mitogens (e.g., Ertl B. et al., J. Drug Target 8:173-84, 2000), neurotransmitters (e.g., During M. J. et al., Ann Neurology 25:351-6, 1989), radioprotectants (e.g., Monig H. et al., Strahlenther Onkol, 166:235-41, 1990), radiosensitizers (e.g., Williams J. A. et al., IJROBP 42:631-39, 1998; and Cardinale R. M. et al., Radiat. Oncol. Invest. 6:63-70, 1998), stimulating and growth factors, transforming agents (e.g., Hong L. et al., Tissue Eng. 6:331-40, 2000), and viral vectors.

Various known methods and seeds relate to the application of heat to a target tissue for the purpose of kitting cancerous cells (see for example Gordon in U.S. Pat. No. 4,569,836 and Delannoy in U.S. Pat. No. 5,284,144). Prior art metallic seeds known as "thermoseeds" have been described by Paulus in U.S. Pat. No. 5,429,583. In contrast to metal thermoseeds that generate heat mainly by eddy current loss, ferromagnetic microspheres generate heat predominantly by hysteresis loss.

Since it is widely known that clinically relevant heating of tissues can be generated by magnetic hysteresis effects, a preferred embodiment includes a magnetically imbued biodegradable carder within the strands/seeds. Widder described an intravascular version of this kind of ferromagnetic microsphere in U.S. Pat. No. 4,247,406. Mitsumori et al. used a dextran-magnetite degradable starch microsphere in their work on inductive hyperthermia in rabbits (Mitsumori et al., *Int J Hyperthermia* 1994; 10:785-93) Minamimura et al., were the first investigator to show significant anti-tumor efficacy in turn bearing rats who were injected with dextran-magnetite microspheres that were then exposed to magnetic forces to generate heat within the tumors (Minamimura et al., *Int. J. Oncol.* 2000; 161153-8). Moroz et al. described successful beating of deep-seated soft tissue in pigs above the critical 42° C. therapeutic threshold following infusions of magnetic iron oxide-doped polymer microspheres (Moroz et al., *J. Surg. Res.* 2002; 105:209-14).

In addition to polymers and starch, other biodegradable substrates can be incorporated into the seeds described herein, as desired by those skilled in the art. Viroonchatapan et al. used thermosensitive dextral-magnetite magnetolipsomes in their in vitro experiments (Viroonchatapan et al, *Pharm. Res.* 1995; 12:1176-83), while Arcos et al. described a new type of biphasic magnetic glass-ceramic mixed with sol-gel glass that has the capability to act as thermoseeds (Arcos et al., *J. Biomed. Mater. Res.* 2003; 65A:71-8).

The claimed brachytherapy seed or strand may also be used for local cancer therapy. In a preferred embodiment, oxygen, hemoglobin, synthetic hemoglobin-like substances, and drugs that enhance tissue oxygen perfusion are included in the biodegradable substrate. Iwashita described a polymer oxygen carrier in U.S. Pat. No. 4,412,989. Bonaventura described a polymeric hemoglobin carrier in U.S. Pat. No. 4,343,715, and Chang described a biodegradable polymer containing hemoglobin in U.S. Pat. No. 5,670,0173. Kakizaki et al. reported on a lipidheme synthetic microspheric oxygen carrier that released oxygen in tissue in vivo (*Artif. Cells. Blood Substit. Immobil. Biotechnol.* 1994; 22:933-8). Bobofchak et al. recently published their work on a recombinant polymeric hemoglobin designated Hb Minotaur (*Am. J. Physiol. Heart. Circ. Physiol.* 2003; 285:H549-61). Substances that can increase oxygen tension in tissue, include but are not limited to oxygen, L-arginine, papaverine, pentoxifyiline, nicotinamide, and nitric oxide and various vasodilators.

Diagnostic compounds can be magnetic (detectable by MRI), radioopaque (detectable by x-ray), fluorescent (detectable by fluorescent techniques) or ultrasound detectable. These materials are commerically available, as are the systems for detection and measurements.

Radiopaque marker **30** can be made of any substance that can be detected by conventional X-ray imaging techniques. See, e.g., *Fundamentals of Diagnostic Radiology,* 2d ed., William E. Brant and Clyde A. Helms (eds.), Lippincott, Williams and Wilkins, 1999; *Physical Principles of Medical Imaging,* 2d ed., Perry Jr. Sprawls, Medical Physic Publishing, 1995; *Elements of Modern X-ray Physics*, Jens Als-Nielsen and Des McMorrow, Wiley & Sons, 2001; *X-ray and Neutron Reflectivity: Principles and Applications*, J. Daillant et al., Springer-Verlag, 1999; *Methods of X-ray and Neutron Scattering in Polymer Science*, Ryoong-Joon J. Roe, Oxford University Press, 2000; and *Principles of Radiographic Imaging: An Art & A Science*, Richard R. Carlton, Delmar Publishers, 2000. Many such substances that can be used as marker **30** are known including, most notably, high atomic number (i.e., "high Z") elements or alloys or mixtures containing such elements. Examples of these include platinum, iridium, rhenium, gold, tantalum, bismuth alloys, indium alloys, solder or other alloys, tungsten and silver. Many currently used radiopaque markers that might be adapted for use in the seeds described herein include platinum/iridium markers from Draximage, Inc. and International Brachytherapy; gold rods from Bebig GmbH; gold/copper alloy markers from North American Scientific, palladium rods from Syncor; tungsten markers from Best industries; silver rods from Nycomed Amersham; silver spheres from International Isotopes Inc. and Urocor; and silver wire from Implant Sciences Corp. Other radiopaque markers include polymers impregnated with various substances (see, e.g., U.S. Pat. Nos. 6,077,880; 6,077,880; and 5,746,998). Radiopaque polymers are described in European Patent Application 894, 503 filed May 8, 1997; European Patent Application 1,016,423 filed Dec. 29, 1999; and published PCT application WO 96/05872 filed Aug. 21, 1995. Those radiopaque polymers that are biodegradable are preferred in applications where it is desired to have the e implant degrade over time in the implantation site.

Examples of radiopaque markers include platinum, iridium rhenium, gold, tantalum, bismuth, indium, tungsten, silver, or a radiopaque polymer. Suitable radioisotopes include ^{125}I and ^{103}Pd.

Sometimes combinations of agents may provide enhanced results. For example, in preferred embodiment, a radiosensitizing agent such as 5-FU, etanidazole, tirapazamine, or BUdR, can be used in combination with IUdR. Various combinations of substances are know to be more effective when used in combination than when used alone. See, e.g, Brem et al., *J. Neurosurg.* 80:283-290, 1994; Ewend et al., *Cancer Res.* 56:5217-5223, 1996; Cardinale, *Radiation Oncol. Investig.* 6:63-70, 1998; Yapp et al., *Radiotherapy*

and Oncol. 53:77-84, 1999; Yapp, IJROBP 39:497-504, 1997; Yuan et al., *Radiation Oncol. Investig.* 7:218-230, 1999; and Menei et al., *Cancer* 86:325-130, 1999.

In addition to the biodegradable radiopaque market in the seeds/strands, microbubbles may also be incorporated to facilitate ultrasonic detection. Micrometer-sized bubbles are known to be extremely potent scatterers of diagnostic frequencies, as reported by Hilgenfeldt et al. in *Ultrasonics* 2000; 38:99-104. Microbubble manufacturing is outlined by Schutt in U.S. Pat. No. 6,280,704 B1 and Schneider in U.S. Pat. No. 6,485,705 B1. The biodegradable microbubble substrate may be disposed within the seed or strand or on any or all of the outer aspect of the invention,

II. Formation of Polymeric Seeds

Although described in this application with especial reference to the formation of polymeric strands, it is understood that the same or similar technology can be used to make strands of the inorganic materials referenced above.

In one embodiment, polylactic acid strands can be fabricated using methods including solvent evaporation, hot-melt microencapsulation and spray drying. Polyanhydrides made of bis-carboxyphenoxypropane and sebacic acid or poly (fumaric-co-sebacic) can be prepared by hot-melt microencapsulation. Polystyrene strands can be prepared by solvent evaporation. Hydrogel strands can be prepared by dripping a polymer solution, such as alginate, chitosen, alginate/polyethylenimine (PEI) and carboxymethyl cellulose (CMC), from a reservoir though microdroplet forming device into a stirred ionic bath, as disclosed in WO 93/21906.

One or more diagnostic, therapeutic or prophylactic compound can be incorporated into the polymeric strands either before or after formation.

Solvent Evaporation

Methods for forming strands using solvent evaporation techniques are described in E. Mathiowitz et al., *J. Scanning Microscopy,* 4:329 (1990); L. R. Beck et al., *Fertil. Steril.,* 31:545 (1979); and S. Benita et al., *J. Pharm. Sci.,* 73:1721 (1984). The polymer is dissolved in a volatile organic solvent, such as methylene chloride. A substance to be incorporated is added to the solution, and the mixture is suspended in an aqueous solution that contains a surface active agent such as poly(vinyl alcohol). The resulting emulsion is stirred until most of the organic solvent evaporated, leaving solid seeds or strands. Seeds and strands with different sizes (1-1000 μm diameter) and morphologies can be obtained by this method. This method is useful for relatively stable polymers like polyesters and polystyrene. However, labile polymers, such as polyanhydrides, may degrade during the fabrication process due to the presence of water. For these polymers, some of the following methods performed in completely anhydrous organic solvents are more useful.

Hot Melt Microencapsulation

Seeds can be formed from polymers such as polyesters and polyanhydrides using hot melt methods as described in Mathiowitz et al., *Reactive Polymers,* 6:275 (1987). In this method, the use of polymers with molecular weights between 3-75,000 Daltons is preferred. In this method, the polymer first is melted and then mixed with the solid panicles of a substance to be incorporated that have been sieved to less than 50 μm. The mixture is suspended in a non-miscible solvent (like silicon oil), and, with continuous stirring, heated to 5° C. above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting seeds are washed by decantation with petroleum ether to give a free-flowing powder. Seeds and strands with diameters between 1 and 1000 μm are obtained with this method.

Solvent Extraction

This technique is primarily designed for polyanhydrides and is described, for example, in WO 93/21906, published Nov. 11, 1993. In this method, the substance to be incorporated is dispersed or dissolved in a solution of the selected polymer in a volatile organic solvent like methylene chloride. This mixture is suspended by stirring in an organic oil, such as silicon oil, to form an emulsion. Seeds that range between 1-300 μm can be obtained by this procedure.

Spray-Drying

Methods for forming seeds using spray drying techniques are well known in the art. In this method, the polymer is dissolved in an organic solvent such as methylene chloride. A known amount of a substance to be incorporated is suspended (insoluble agent) or co-dissolved (soluble agent) in the polymer solution. The solution or the dispersion then is spray-dried. Seeds ranging between 1 and 10 μm are obtained. This method is useful for preparing seeds tot imaging of the intestinal tract. Using the method, in addition to metal compounds, diagnostic imaging agents such as gases can be incorporated into the seeds.

Phase Inversion

Seeds can be formed from polymers using a phase inversion method wherein a polymer is dissolved in a good solvent, fine particles of a substance to be incorporated, such as a drug, are mixed or dissolved in the polymer solution, and the mixture is poured into a strong non-solvent for the polymer, to spontaneously produce, under favorable conditions, polymeric seeds, wherein the polymer is either coated on the particles or the particles are dispersed in the polymer. The method can be used to produce microparticles in a wide range of sizes, including, for example, about 100 nm to about 10 μm. Exemplary polymers which can be used include polyvinylphenol and polylactic acid. Substances which can be incorporated include, for example, imaging agents such as fluorescent dyes, or biologically active molecules such as proteins or nucleic acids.

Protein Microencapsulation

Protein seeds can be formed by phase separation in a non-solvent followed by solvent removal as described in U.S. Pat. No. 5,271,961 to Mathiowitz et al. Proteins which can be used include prolamines such as zein. Additionally, mixtures of proteins or a mixture of proteins and a bioerodable material polymeric material such as a polylactide can be used. In one embodiment, a prolamine solution and a substance to be incorporated are contacted with a second liquid of limited miscibility with the prolamine solvent, and the mixture is agitated to form a dispersion. The prolamine solvent then is removed to produce stable prolamine seeds without crosslinking or heat denaturation. Other prolamines which can be used include gliadin, hordein and kafirin.

Low Temperature Casting of Seeds

Methods for very low temperature casting of controlled release seeds are described in U.S. Pat. No. 5,019,400 to Gombotz et al. In the method, a polymer is dissolved in a solvent together with a dissolved or dispersed substance to be incorporated, and the mixture is atomized into a vessel containing a liquid non-solvent at a temperature below the freezing point of the polymer-substance solution, which freezes the polymer droplets. As the droplets and non-solvent for the polymer are warmed, the solvent in the droplets thaws and is extracted into the non-solvent, resulting in the hardening of the seeds.

Strands can also be made using many of the above-techniques using extrusion technology to elongate the seeds into strands.

Hydrogel Seeds

Seeds made of gel-type polymers, such as alginate, are produced through traditional ionic gelation techniques. The polymer first is dissolved in an aqueous solution, mixed with a substance to be incorporated, and then extruded through a microdroplet forming device, which in some instances employs a flow of nitrogen gas to break off the droplet. A slowly stirred ionic hardening bath is positioned below the extruding device to catch the forming microdroplets. The seeds are left to incubate in the bath for twenty to thirty minutes in order to allow sufficient time for gelation to occur. Particle size is controlled by using various size extruders or varying either the nitrogen gas or polymer solution flow rates.

Chitosan seeds can be prepared by dissolving the polymer in acidic solution and crosslinking it with tripolyphosphate. Carboxymethyl cellulose (CMC) seeds can be pared by dissolving the polymer in acid solution and precipitating the microsphere with lead ions. Alginate/polyethylene imide (PEI) can be prepared in order to reduce the amount of carboxylic groups on the alginate microcapsule. The advantage of these systems is the ability to further modify their surface properties by the use of different chemistries. In the case of negatively charged polymers (e.g. alginate, CMC), positively charged ligands (e.g., polylysine, polyethyleneimine) of different molecular weights can be ionically attached.

Fluidized Bed

Particles, including seeds, can be formed and/or coated using fluidized bed techniques. One process is the Wurster air-suspension coating process for the coating of particles and seeds. The process consists of supporting the particles in a vertical column of heated air while the particles pass an atomizing nozzle that applies the coating material in the form of a spray. Enteric and film coating of seeds or strands by this process typically requites approximately 30 minutes. Suitable coating materials include, but are not limited to, cellulose acetate phthalate, ethylcellulose, hydroxypropyl methylcellylose, polyethylene glycol, and zein.

The Wurster apparatus provides controlled cyclic movement of the suspended particles by a rising stream of warm air, the humidity, temperature, and velocity of the air regulated. Art air-suspended or fluidized bed of particles has a random movement. If seeds or strands move in and out of a coating zone in a random manner, the coating can be applied only at a slow rate. The Wurster apparatus, however, provides better drying and eventually a more uniform coating by imparting a controlled cyclic movement without or with less randomness. A support grid at the bottom of the vertical column typically includes a course screen, e.g., 10 mesh, and a fine screen, e.g., 200 mesh. The fine screen offers considerably more resistance to the air flow than the coarse screen; thus, the greater amount of air flows through the coarse screen. The air flowing through coarse screen lifts the seeds or strands upward in the column. As the velocity of the air stream is reduced due to diffusion of the stream and resistance of the seeds or strands, the upward movement of the seeds or strands ceases. Then the seeds or strands enter the region of a still lower velocity air stream above the fine screen, where they dry and gently settle. As the dried and partially coated seeds or strands approach the grid, they are again introduced into the higher-velocity air stream and the coarse screen, and enter into another cycle.

Below the grid support for the coarse screen, the coating fluid is dispersed by atomization under pressure. A compressed-air inlet is connected to the atomizing the solution or slurry of the coating material. The seeds or strands, which are suspended above the coarse screen, have little contact with each other, so the coating fluid is readily distributed onto the surface of the seeds or strands in the moving bed. As the cyclic movement of the seeds or strands continues, the seeds or strands are presented many times in many different positions to the atomized spray; therefore, a uniform coating is built up on the seeds or strands. Coating is controlled by the weight of the coated seeds or strands, formulation of the coating, temperature, time, and air velocity. Particle sizes can vary from about 50 μm to about 2 mm or greater.

IV. Method of Making Brachytherapy Strand for Implantation

One method of making a brachytherapy strand for implantation into a subject includes the steps of: (a) providing a non-metal biocompatible component and a therapeutically active diagnostic or prophylactic component (herein referred to as "therapeutically active component"), optimally further including an imaging agent or tracer; (b) physically associating the biocompatible component and the therapeutically active component to from a combination product; and (c) forming the combination product into a strand having a size and shape suitable for passing through the bore of a needle having an interior diameter of less than about 2.7 millimeters (10 gauge), less than about 1.4 millimeters (15 gauge), or less than about 0.84 millimeters (18 gauge), or less than about 0.56 millimeters (24 gauge).

Referring to the drawings the are illustrated various different embodiments of the brachytherapy strands. Although there is no lower limit as to how small any dimension of strand can be, in many applications, those that are not able to pass through bores smaller than 0.3 mm are preferred. For example, in many applications where it is desirable for the implanted brachytherapy strands to maintain their orientation in the tissue, the strand should be large enough to stay lodged at the site of implantation in the desired orientation for a relatively long period, larger strands are preferred. In some cases, the selection of materials for use in the strand will affect its size. For instance, in versions of the strand where the biocompatible component is a stainless steel or titanium capsule, the walls of the capsule may need to be greater than a certain minimum size in order to maintain the structural integrity of the strand. In addition, in some applications, the strand should also be large enough to carry a sufficient amount of the therapeutically active component to be therapeutically active (i.e., a therapeutically effective amount or an amount that exerts a desired medically beneficial effect). In order to facilitate the passage of the strand through the bore of a needle while preventing jamming of the brachytherapy implantation needle bore (e.g., caused by clumping of several strands), it is also preferred that the diameter of strand be just slightly less than the diameter of the bore of the needle (e.g., 0.5-5% less).

For use with the needles used in many conventional brachytherapy strand implantation devices, brachytherapy seeds shaped into a cylinder (or rod) having a diameter of between about 0.8 to 3 millimeters and a length of up to 40 millimeters are preferred. Because many conventional brachytherapy strand applicators make use of brachytherapy implantation needles about 17 to 18 gauge in size, cylindrically shaped brachytherapy strands having a diameter of between about 0.8 and 1.1 mm and a length greater than the diameter (e.g., 2-10 mm) are preferred for use with such

applicators. In particular, because many conventional brachytherapy strand applicators are designed to accept conventional radioactive brachytherapy strands that have a diameter of about 0.8 millimeters and a length of about 4.5 millimeters, brachytherapy strands of similar size are especially preferred.

Brachytherapy strands are not limited to those being cylindrical in shape, but rather can be any shape suitable for passing through the bore of a needle. For example, in any cases, the cross-sectional area of the strands can be cuboid, spheroid, ovoid, ellipsoid, irregularly shaped, etc. The ends of the strands can be rounded, squared, tapered, conical, convex, concave, scalloped, angular, or otherwise-shaped. The brachytherapy strands can be solid or have one or more cavities or pores (e.g., to increase the surface area of the strand exposed to the target tissue).

FIG. **1** is a schematic side view of a cylindrically shaped brachytherapy strand. FIG. **2** is a schematic side view of a hollow tube-shaped brachytherapy strand.

As one example, as illustrated in FIG. **2**, a brachytherapy strand **10** is shaped into a hollow tube **18** having a cylindrical cavity **20**. In preferred versions of strand **10**, cylindrical cavity **20** is sized to accept and envelop a standard-sized brachytherapy strand (e.g., one having a diameter of about 0.8 mm and a length of about 4.5 mm). For use, the strand **10** can be placed over the standard-sized brachytherapy strand, and introduced into the bore of a needle (sized to accept the enveloped strand) for implantation into a target tissue. The strand **10** shown in FIG. **2** can also be used alone without being placed over a standard-sized brachytherapy strand, e.g., to increase the surface area exposed in the site of implantation. Hollow tube **18** can have any wall thickness or length suitable for wholly or partially enveloping a standard-sized brachytherapy strand and passing through the bore of a needle. Preferably it has a wall thickness between about 0.01 and 0.1 mm and a length of between about 1 to 4.5 mm.

Referring again to FIGS. **1** and **2**, biocompatible component **12** can be composed of any material suitable for implantation in a target tissue in an animal subject (e.g., a mammal such as a human patient) that can be associated with therapeutically active component such that all or part of the therapeutically active component will be delivered to the target tissue when the brachytherapy strand **10** is introduced into the implantation site, as discussed above. For ease of use, ease of manufacture, and for therapeutic advantages, it is preferred that the biocompatible component **12** be biodegradable (i.e., made of a substance other than titanium or stainless steel).

A skilled artisan can select the particular composition of the component **12** that is most suited for a given application. For example, where the strand **10** is intended to be used to slowly deliver the therapeutically active component **14** when implanted in a target tissue, a biocompatible and biodegradable material made up of a chemical composition of a polymer known to degrade at a desired rate when placed under conditions similar to those encountered in the implantation site can be selected for use as component **12**. Various characteristics of such biodegradable components are described, e.g., in *Biomaterials Engineering and Devices: Human Applications: Fundamentals and Vascular and Carrier Applications*, Donald L. Wise et al. (eds), Humana Press, 2000; *Biomaterials Science: An Introduction to Materials in Medicine*, Buddy D. Ratner et al. (eds). Academic Press, 1997; and *Biomaterials and Bioengineering Handbook*, Donald L. Wise, Marcel Dekker, 2000. For example, by selecting an appropriate material for use as the biocompatible component **12** of the brachytherapy strand **10**, the duration of release of the therapeutically active component **14** from strand **10** can be varied from less than about an hour to more than about several months (e.g., 10 min., 30 min., 1 h., 2 h., 3 h., 6 h., 12 h., 1 day, 2 days, 3 days, 1 week, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 1 year, 2 years, or 3 years). Biocompatible component **12** is not limited to being biodegradable. For example, in some cases, component **12** can also be made of a non-biodegradable material such as stainless steel or titanium. In this case, biocompatible component **12** can be coated or otherwise associated with therapeutically active component **14**, such that component **14** will be delivered to a target tissue into which strand **10** is implanted. For instance, component **12** might take the form of a porous stainless steel or titanium cylinder having a plurality of pores through its outer surface, such pores being filled with or otherwise in communication with the component **14** such that the component **14** can diffuse from the strand **10** into the environment surrounding the strand **10** (e.g., a target tissue).

These can be tested for suitability in a given application by conventional clinical testing. For example, a test composition can be fashioned into a brachytherapy strand and implanted in a laboratory animal in a selected target tissue. The effects of the implanted compositions on the animal can then be monitored over a period of time. Those that prove to be biocompatible (e.g., not causing an undesired response such as calcification or an allergic response) and have a desired rate of degradation and delivery of a therapeutically active component (if included in the test strand) can thus be identified.

As discussed above, the therapeutically active component **14** is a material that can be (a) implanted in a target tissue of an animal subject (e.g., a mammal such as a human patient) to exert an effect on the animal's physiology, and (b) associated with the biocompatible component **12** in the brachytherapy strand **10**. Myriad different substances can be used as the therapeutically active component **14**. See, e.g., Physician's Desk Reference, The Merck Index, and USP DI® 2000 published by U.S. Pharmacopeia. For example, the therapeutically active component **14** can include a small molecule drug (e.g., a non-peptide or non-nucleic acid-based molecule with a molecular weight generally less than 5 kDa) such as a chemical with known anti-cancer properties. It can also include a biologic such as a polypeptide (e.g., an antibody or a cytokine) or nucleic acid (e.g., an expression vector). For example, where the strand **10** is intended to be used as a primary treatment for prostate cancer, the therapeutically active substance **14** can include an anti-neoplastic drug such as paclitaxel (taxol), cisplatin, or 5-fluorouracil; or a hormone such as leuprolide. As another example, whole the strand **10** is intended to be used as an adjuvant to radiation treatment for prostate cancer, the therapeutically active substance **14** can include a radio-sensitizing agent such as tirapazamine, BUdR, IUdR, or etanidazole. Because brachytherapy strand **10** allows in situ drug delivery to a tissue, the therapeutically active substance **14** may include a drug that is usually considered too toxic to treat a given condition if given systemically, e.g., tirapazamine or camptothecin.

As indicated in the above description of the brachytherapy strand **10** shown in FIGS. **1** and **2**, the biocompatible component **12** is associated with the therapeutically active component **14**. As used herein, when referring to the biocompatible component **12** and the therapeutically active component **14**, the phrase "associated with" means physically contacting. Thus, in the strand **10**, the association of the

biocompatible component **12** with the therapeutically active component **14** can take many forms. For example, the biocompatible component **12** and the therapeutically active component **14** can be combined into a mixture as shown in FIGS. **1** and **2**. This mixture can have a uniform or non-uniform distribution of components **12** and **14**. The brachytherapy strand **10** shown in FIG. **1** is an example of a uniform mixture of components **12** and **14**. The brachytherapy strand **10** of this example can be made by simply mixing together the biocompatible component **12** and the therapeutically active component **14** to form a combination product and then forming the product into the desired size and shape, e.g. using a mold.

Although the brachytherapy strands shown in FIGS. **1** and **2** include mixtures of discrete particles dispersed through a matrix consisting of the therapeutically active component **14**, in other versions of brachytherapy strand **10**, components **12** and **14** are combined in a single particle or in a larger mass without discrete particles (e.g., a pellet the size and shape of brachytherapy strand **10**). For example, biocompatible component **12** and therapeutically active component **14** can be dissolved into a liquid and then dried or cured to form strands or a larger pellet made up of a homogeneous distribution of both components **12** and **14**. (see, e.g., Ramirez et al., *J. Microencapsulation* 16:105, 1999).

The skilled artisan can select the size according to the desired properties and particular properties of the microsphere constituents. In one variation of this, the strands are also made to include magnetic elements. The strands can then be molded or compressed together into the desired shape and size of brachytherapy strand **10**. The larger pellet can likewise be sculpted, extruded, molded or compressed into the desired shape and size of brachytherapy strand **10**. Alternatively, the liquid mixture of components **12** and **14** can be poured into a mold defining the shape and size of brachytherapy strand **10**, and then cured in the mold. Brachytherapy strands having components **12** and **14** combined in a single particle or in a larger mass (rather than discrete particles of each are advantageous for delivering the therapeutically active component **14** into a target tissue over longer time periods.

In other embodiments of strand **10**, components **12** and **14** are not necessarily homogeneously mixed in the strand **10**. Rather they can be positioned in different areas of the strand **10**. For example, components **12** and **14** can be separately fashioned into discrete sections, strips, coils, tubes, etc. The discrete sections, strips, coils, tubes, etc. of the component **12** can then be combined (e.g., by molding together, adhering, structurally interlocking, etc.) with the discrete sections, strips, coils, tubes, etc. of the component **14** to form the strand **10**. In another embodiment, the strand **10** shown in FIG. **2** can be modified by filling the cylindrical cavity **20** with a hydrogel, including a therapeutically active substance, and capping off the ends of the hollow tube **18**.

These variations are more clearly understood by reference to the following figures. FIGS. **3**A-**3**I are strands with inert spacers **20**, interspersed for cutting (FIG. **3**A); with pop-up wings **22** to prevent migration or shifting after implanting (FIG. **3**B); with a radiopaque strip **30** running through it (FIG. **3**C); with cross-style stabilizers **32** (FIG. **3**D); with male **34** and female **36** ends to facilitate joining, e.g., in a ring (FIG. **3**E); with indentations **38** for cutting or breaking into smaller strands (FIG. **3**F); with a stabilizer, such as bumps **40** (FIG. **3**G); as braided strand **42** (FIG. **3**H); and strands knotted together **44** (FIG. **3**I). FIGS. **4**A and **4**B are a strand **50** with radioactive seeds **52** interspersed (perspective view, FIG. **4**A; cross-sectional view, FIG. **4**B).

The foregoing combination products (i.e., at least one biocompatible component mixed with at least one therapeutically active component) can be used in the brachytherapy strands by forming them into a size and shape suitable for passing through the bore of a needle such as one in a conventional brachytherapy strand implantation device. Referring now to FIGS. **3**A-I, in others, a brachytherapy strand **10** includes a biocompatible component **12** associated with a therapeutically active component **14**, and a radiopaque marker **30** (not shown except in FIG. **3**C) attached to the biocompatible component **12** and/or the therapeutically active component **14**. Radiopaque marker **30** allows for the position of brachytherapy strand **10** to be determined using standard X-ray imaging techniques (e.g., fluoroscopy) after strand **10** has been implanted in a target tissue. Proper positioning of strand **10** and spacing of a plurality of brachytherapy strands in a given target tissue is important for ensuring that the therapeutically active component **14** is delivered adequately to the site of the disease in the target tissue.

As indicated above, radiopaque marker **30** is attached to strand **10** via the biocompatible component **12** and/or the therapeutically active component **14**. The exact manner in which radiopaque marker **30** is attached to strand **10** can is not critical so long as (a) the strand **10** can be passed through the bore of a brachytherapy implantation needle and (b) the attachment allows the position of strand **10** to be readily detected by X-ray imaging. A description of some different examples of how marker **30** can be associated with strand is presented in FIGS. **3**A-F. In the embodiment shown in FIG. **3**A, the radiopaque marker **30** in the form of a ribbon, filament, strip, thread, or wire is placed in the center and along the length of cylindrical strand **10**. In FIG. **3**B, the radiopaque marker **30** takes the form of two end caps placed at both ends of cylindrical strand **10**. In the embodiment illustrated in FIG. **3**C, the radiopaque marker **30** is a coil made of a radiopaque substance running through the length of cylindrical strand **10** as shown. In FIG. **3**D, the radiopaque marker **30** takes the form of two beads or pellets placed at two locations along cylindrical strand **10**. In the embodiment shown in FIG. **3**E, the radiopaque marker **30** takes the form of two bands or rings placed at two locations along the outer surface of cylindrical strand **10**. In the strand **10** shown in FIG. **3**F, the radiopaque marker **30** takes the form of a mesh formed into cylindrical shape. In the strand **10** shown in FIG. **3**G, the radiopaque marker **30** is dispersed throughout the strand in a stippled pattern.

FIGS. **4**A and **4**B are a strand with radioactive seeds interspersed (perspective view, FIG. **4**A; cross-sectional view, FIG. **4**B).

A particularly preferred embodiment of a brachytherapy strand having a radiopaque marker is one in which the radiopaque marker is a polymer. In one version of this embodiment, radiopaque polymers are combined with a biocompatible component and a therapeutically active component to form a brachytherapy strand that can be visualized by X-ray imaging. Alternatively, the radiopaque polymer can serve as the biocompatible component. For example, strands made of a radiopaque polymer are co-mingled with strands containing a biocompatible component and strands containing (e.g., encapsulating) a therapeutically active component for strands containing both a biocompatible component and a therapeutically active component). The co-mingled strands are then molded into a radiopaque brachytherapy strand. As another example, the radiopaque

polymer, the biocompatible component, and the therapeutically active component can be mixed together into a liquid, and the liquid can be cured to form a solid pellet that can be sculpted, molded, compressed, or otherwise made into the size and shape of a brachytherapy strand. An advantage of preparing a radiopaque brachytherapy strand in this manner is that, after implantation, the entire strand can be visualized by X-ray imaging rather than only a portion of a strand (e.g., as occurs with strands utilizing conventional markers).

FIGS. **5**A-**5**D are perspective views of strands after introduction into breast adjacent to lumpectomy site (larger circle) below the nipple (smaller circle) (FIG. **5**A); strands conforming to shape of breast with patient now upright, lumpectomy site is shown as larger black circle, nipple as smaller circle (FIG. **5**B); strand deployed as a coil (FIG. **5**C); and strands deployed as rings around lumpectomy site (FIG. **5**D).

FIG. **6** is a magnified depiction of microfabricated polyimide hairs. By covering the brachytherapy seed or strand with these polyimide hairs, the problem of seed migration can be effectively overcome. Seed migration involves movement of seeds from their implanted location, usually during the interval immediately following wed placement. Two precipitating causes are felt to be a recoil effect in tissue as it springs back from deformation caused by the seed introducer needle, and suction along the exit path caused by the needle as it is withdrawn after depositing seeds. Several papers in the literature have addressed this issue (see for example, Tapen et al., *IJROBP* 1998; 42:1063-7, Merrick et. al., *IJROBP* 2000; 46:215-20, Poggi et al., *IJROBP* 2003; 56:1248-51).

One method of overcoming this problem is to secure seeds together in a coaxial array within suture strand material such that seeds are kept at a fixed distance from one another. Another approach is to attach each seed to an interlocking peg (see Grimm U.S. Pat. No. 6,450,939B1), again to create a fixed arrangement. However, these systems are fixed by definition, and can present logistical problems when one is working with irregularly shaped targets, or targets that are split by intervening tissue that one wishes to avoid. Furthermore, the strands themselves can migrate, skewing the dosimetry for an entire row of seeds.

Prior art brachytherapy seeds have not satisfactorily addressed the issue of limiting individual seed movement along the needle track. Giem et al have succeeded in producing microfabricated polyimide hairs, and showed that their artificial hairs produce capillary and van der Waals forces which impart particular adhesive properties (Giem et al., *Nature Materials* 2003; 2:461-3). These polyimide hairs have been constructed based on the structure of gecko foot-hairs (setae) which have been shown to have astounding adhesive properties. The polyimide hairs have diameters from 0.2-4 micrometers, heights from 0.15-2 micrometers, and periodicity from 0.4-4.5 micrometers.

The hairs were made as long as possible, and have sufficient flexibility so that individual tips can attach to uneven surfaces all at the same time, and do not break, curl or tangle. Care was taken not to make the hairs too thin, lest they fall down, or too dense, lest they bunch. In order to overcome the problems associated with seed and strand migration, setae technology is used to cover or coat the biodegradable seeds and strands with hairs that impart comparable adhesive potential.

When seeds and strands are implanted into tissues, those tissues are unevenly distributed around the implanted material. The compliant setal structure permits conformance to the shape of a contacting structure, increasing the magnitude of the attractive van der Waals forces as the tiny hairs act together. Similarly, as the seeds and strands are pushed out of their introducing needle, they are dragged over the tissue, which increases setal adhesion. Larger setae create larger sticking forces from larger setal contact areas.

Finally, the tissue is moist since it is living tissue, and setae have improved adhesive properties when they are moist. All of these factors make biodegradable setae (protrusions) an ideal solution to seed/strand migration [see FIG. **6**].

FIGS. **7**A and **7**B illustrate brachytherapy strand geometries such that the brachytherapy strand has one or more conduits running along the length of the strand. These conduits can be pre-filled or fillable, and are useful in the delivery of therapeutic and diagnostic agents to the surrounding implanted tissue. The agents need not be biodegradable themselves, but should be fluid enough to pass through the conduits. Optionally, there can be a pore, series of pores, or network of pores and conduits along the strands through which the agents flow out into the surrounding tissue. In another embodiment, there can be a portal that can be accessed with a needle or other introducer instrument through the skin, or the portal can protrude out of the body via a percutaneous connection to the conduit system. The radioactive material in the strand, if present, can be separated from the conduit system by intervening non-radioactive material. Sundback et al described a similar system in *Biomaterials* 2003; 24:819-30 wherein the conduits were used to contour nerve growth.

The therapeutically active agent **14** in strand **10** including the sealed container **40** can be any of those agents described above. Preferably, however, agent **14** is selected to provide an enhanced effect when used in combination with the radioisotope to treat a particular diseased tissue, as discussed above.

The radioisotope can be any substance that emits electromagnetic radiation (e.g., gamma-rays or X-rays), beta-particles or alpha particles and is suitable for use in brachytherapy strand **10**. Examples of such substances include those that decay principally by electron capture followed by X-ray emission such as palladium-103 and iodine-125; isotopes that decay by the emission of beta-particles such as gold-198, gold-199, yttrium-90, and phosphorus-32; isotopes that decay with the emission of both beta-particles and gamma-rays such as indium-192; and isotopes that decay with the emission of alpha-particles such as americium-241. Also useful is gadolinium-157, e.g., for use in boron-neutron capture therapy, and californium-252, rhenium-188, samarium-153, indium-111, ytterbium-169, and holmium-166. For the treatment of prostate cancer, palladium -103 and iodine-125 are preferred as these have been the subject of much clinical investigation for the treatment of the disease. The amount of radioactivity of radioisotope can vary widely. For example, when using palladium-103 or iodine-125, an exemplary amount to treat prostate cancer is respectively about 1.5 mCi and 0.33 mCi per strand, if about 50-150 strands are used at the time of implantation. In other applications the radioactivity per strand can range from about 0.01 mCi to about 100 mCi.

In one embodiment, the radioisotope can be mixed with and then configured into strands, or it can be encapsulated by the biocompatible component to form strands. The radioactive strands cart be molded or otherwise sized and shaped into a brachytherapy strand suitable for implantation via a brachytherapy implantation device. In one version of this embodiment, the biocompatible component is biodegradable such that the radioisotope contained by this component is

gradually released from the strand. Alternatively, the biocompatible component and radioisotope can be mixed together and configured as an amorphous pellet having the size and shape of a brachytherapy strand suitable for implantation via a brachytherapy implantation device.

In a preferred embodiment in which the brachytherapy strand contains radionuclide, the strand is coated with a non-radioactive biodegradable coating which degrades at a rate slower than that which allows the radioactivity to leach out, so that radioactivity is not released—i.e., the radioactivity has already fully decayed.

FIGS. **8**A, **8**B and **9** depict the addition of polymeric anchoring structures to brachytherapy strands. Biodegradable seeds may also be equipped with as similar system, but on a smaller scale. As noted above, migration can be problematic. Built-in ridges, bumps, and related structures can ameliorate this problem to some extent, but will not completely eliminate it.

Biodegradable shape memory polymeric (Lendlein et al., *Science* 2002; 296:1673-6) structures which deploy to their pre-trained shape after implantation in order to maintain the seeds in the desired location may also be used. Such structures can ideally include grapple-shaped anchors at the ends of a brachytherapy strand [see FIG. **8**A]. These hooks deploy following introduction of the strand into the target tissue. Similar structures can be interspersed the length of the strand, oriented such that the strand becomes locked in position [see FIG. **8**B]. The same concept can be used to brace or center the strands within a target tissue in instances where that tissue contains a cavity, defect or other irregular space that might otherwise kink, bend, or offset the strand [see FIG. **9**].

These may be bristle-like, ring-shaped, or alternative shapes depending upon the choice made by those skilled in the art. Similarly, they can space apart adjacent strands, thereby avoiding clumping or bunching. Optionally, these structures may or may not contain the therapeutic or diagnostic agents. The shape memory structures are activated by heat from the implanted tissue, or are preheated prior to implantation to trigger their deployment.

As with the shape memory polymer above, electroactive polymers (EAPs) or polymer hybrids may be used for stabilization, spacing, or related purposes. Hybrid substrates can include biodegradable polymer/semiconductor composites. These components expand, contract, bend, or otherwise change shape or size displacement upon exposure to an applied voltage. These types of changes can be induced with very low voltage input which can be achieved without harming the host tissue. Pelrine described this style device in U.S. Pat. No. 6,545,384 B1, as did Kombluh in U.S. Pat. No. 6,586,859B2.

Electronic EAPs can include ferroelectric polymers, dielectric polymers, electrorestrictive graft elastomers, electro-viscoelastic elastomers, liquid crystal elastomer materials, or other related polymers or organic substances. Ionic EAPs can include ionic polymer gels, ionomeric polymer-metal composites, conductive polymers, carbon nanotubes, or other related polymers or organic substances (see for example Bar-Cohen et al., ed., *Electroactive Polymers and Rapid Prototyping: Materials Research Society Symposium Proceedings*, Materials Research, 2002; *Applications of Electroactive Polymers*, (Stienen, ed.), Kluwer Academic Publishers, 1993; Zhang et al., *Nature* 2002; 419:284-7). Scheibel et al. described the use of biomolecular templates as conducting nanowires in *PNAS* 2003; 100:4527-32. In this instance, amyloid formed by prions was the biomolecular substance used to create the nanowires. Various physicochemical factors, such as light, temperature, and pH can be applied to the "small polymers" or other substrates to achieve similar configuration modification.

Spacers can be made of a biocompatible material that can be used to join two brachytherapy seeds. See, e.g., U.S. Pat. No. 6,010,446. The biocompatible material can be either biodegradable or non-biodegradable. For example, spacers can be made of catgut or a like materials. Spacers designed for use with conventional radioactive brachytherapy seeds can be used in chain. For example, Ethicon, Inc. (Cincinnati, Ohio) manufactures the PG 940 non-sterile autoclavable spacer for Indigo (Cincinnati, Ohio) that is sold in conjunction with an Express Seed Cartridge. In addition, Medical Device Technologies, Inc. (Gainesville, Fla.) distributes a pre-sterilized 5.5 mm long absorbable pre-cut spacer that is made of collagen (Look®, model number 1514b). Materials for use as the spacer are also manufactured by Surgical Specialties Corp. (Reading Pa.). Where the spacer is made of a relatively flexible material, the chain can be relatively flaccid.

Where the brachytherapy strand or linker is formed of an elastic polymer such as elastin-like peptides, polyhydroxyalkanoates (PHAs) or poly(glycol-sebacate), or some protein, the strand or chain is becomes high deformable. Such deformability is particularly advantageous when implanting tissues or organs whose shape may become distorted by normal body motion, such as the breasts or viscera. Where the chain is endowed with the flexibility of an elastic polymer or similar substance, the chain may be considered to be variably flexible rather than rigid or flaccid. The precise degree of flexibility will depend upon the composition of the carrier matrix. Those skilled in the art will be accustomed to selecting the ration of component substances in the carder matrix such that the desired degree or flexibility is achieved. This flexibility, rather than being simply linear or curved, can be in any direction. In some embodiments, the chain may be spiral-shaped or otherwise twisted, springy, or bent to conform to the desired shape. In other embodiments, the chain can form a lattice or mesh whereby one or more chains can be interconnected through baking mechanisms, knots ties, welds, fusions, or other methods known to those skilled in the art. In yet another embodiment, the chain may be introduced into the target tissue in one shape, only to be purposefully or intentionally modified or altered to another advantageous shape thereafter.

Spacers can be connected to seed by any means known. For example, spacer can be connected to seed by direct attachment such as by gluing, crimping, or melting. Spacers can be attached to any portion of the seed. For rod or cylinder-shaped seeds, to facilitate implantation, it is generally preferred that spacers are attached to the ends of the seeds so that the ends are adjacent to one another when the chain is inserted into the barrel of a brachytherapy implantation needle. In one preferred embodiment, the spacer and seed are indistinguishably linked such that no seams, welds, or joints are visible. In another embodiment, the spacer may be of a different color, texture, diameter, hardness, or shape for easy identification and demarcation. This can include a translucent coloration. In still another embodiment, the spacer may be indented or otherwise marked somewhere along its length as an indication of where the seed/spacer chain can be safely cut, spliced, broken, or otherwise separated without exposing active therapeutic substances such as radionuclides that are contained within the seed.

In another embodiment, spacers may be emitted in favor of a continuous array of seeds that may form a chain or strand. This is especially advantageous when implanting an

organ such as the breast, where discrete seeds are not necessarily required to achieve the desired dispersement of radioactivity and/or other therapeutic substances. The continuous seed array without interruption by spacer is especially preferred when the implanted strands contain an elastic polymer or other flexible carder for use in a mobile organ or tissue. In yet another embodiment, spacers may be located at varying distances from one another, separated by different lengths of continuous seed arrays, depending upon the clinical circumstances. Depending upon the discretion of the clinician, more than one continuous seed and/or spacer array may be implanted along a given row to achieve the desired effect in tissue.

Where spacers are used, spacer and seed, however, need not be physically attached to each other. Rather they can also be associated with each other by placing each with within the lumen of a tube. The tube can be used to load a brachytherapy seed implantation device with a plurality of spacers and seeds in any sequence. For example, the brachytherapy seed implantation device can loaded with one (or 2, 3, 4, 5, or more) spacer being interposed between every two seeds. Similarly, the brachytherapy seed implantation device can be loaded with one (or 2, 3, 4, 5, or more) seed being interposed between every two spacers.

VI. Methods of Implantation

The brachytherapy strands are implanted into a target tissue within a subject (e.g., a human patient or a non-human animal) by adapting known methods for implanting conventional radioactive brachytherapy seeds into a tissue. For example, the brachytherapy strands can be implanted using one or more implantation needles; Henschke, Scott, or Mick applicators; or a Royal Marsden gold grain gun (H. J. Hodt et al., *British J. Radiology*, pp. 419-421, 1952). A number of suitable implantation devices are described in, e.g., U.S. Pat. Nos. 2,269,963; 4,402,308; 5,860,909; and 6,007,474.

In many applications to treat a given target tissue with a therapeutic agent, it is desirable (or even ideal) to fully saturate the target tissue with the therapeutic agent, while avoiding under- or over-dosing the target tissue. This can be achieved by implanting the brachytherapy strands into a target tissue using a brachytherapy implantation device so that a precise number of strands can be implanted in precise locations within the target tissue. By previously calculating the rate of diffusion of the therapeutically active substance under experimental conditions (e.g., using tissue from animal models), an appropriate dosage can be delivered to the target tissue. Because use of brachytherapy implantation devices allows the brachytherapy strands to be implanted in any number of different desired locations and/or patterns in a tissue, this method advantageous over methods where a drug or drug impregnated matrix is simply placed on the surface of a tissue or manually inserted into a surgically dissected tissue.

In one preferred method of use, the strands are introduced into the target organ through a puncture site with a brachytherapy needle, obviating the need for an incision, suturing of a catheter, tracheostomy, or prolonged insertion of an often uncomfortable or painful metallic or plastic foreign body into the patient. In the case of the base of tongue, the hairpin needles are withdrawn following loading of the strands, thereby limiting the degree of swelling that occurs and possibly sparing the patient the need for a tracheostomy. In the case of a lumpectomy for removal of a beast cancer, the strands can be placed in the same fashion as temporary iridium-192 or iodine-125 metallic seed strands, but without the sutures and buttons anchoring the catheters or needles and strands to the skin retrieval later.

I claim:

1. A flexible non-radioactive strand for implantation into a subject, comprising:

a marker component configured to allow for the determination of the position of the strand within a target tissue, the marker component having a length extending along a centerline of the marker component between a first end and a second end and having a substantially continuous wall bounding a hollow interior; a biocompatible component; and

a therapeutic, prophylactic, and/or diagnostic agent, wherein the marker, biocompatible component and agent are disposed within the hollow interior;

wherein the length of the marker component is greater than the diameter of the hollow interior, and

wherein the substantially continuous wall includes at least one opening adapted to allow the agent to pass out of the hollow interior wherein the strand do not contain a radioisotope.

2. The flexible strand according to claim **1** wherein the marker component has a maximum length of between one and 50 cm.

3. The flexible strand according to claim **2**, wherein the marker component has a maximum length of 40 mm and a diameter between about 0.8 and 3 mm.

4. The flexible strand according to claim **1** wherein at least one of the marker component and the agent is imageable.

5. The flexible strand according to claim **4** wherein the marker component is imageable.

6. The flexible strand according to claim **1** wherein the substantially continuous wall comprises one or more biodegradable structures effective to maintain orientation in tissue, one or more compliant setal or hair structures which impart adhesive properties upon implantation into a target tissue, or combinations thereof.

7. The flexible strand of claim **6**, wherein the structures to maintain location or orientation comprise a smart polymer, a shape memory polymer, or other substrate to achieve configuration modification.

8. The flexible strand according to claim **6** wherein the structures include an anchor.

9. The flexible strand according to claim **1**, wherein the hollow interior comprises a biocompatible component, and wherein the marker component and the agent are dispersed in the biocompatible component.

10. The flexible strand according to claim **1** wherein the agent is intermixed with the marker component.

11. The flexible strand according to claim **10** wherein the marker component is biodegradable.

12. The flexible strand according to claim **9** wherein the biocompatible component is configured to degrade over time at the implantation site and release the agent by controlling the rate of degradation and/or release rate at the implantation site.

13. The flexible strand according to claim **1** wherein the marker component comprises a high Z material.

14. The flexible strand according to claim **1** wherein the at least one opening comprises the first and/or second ends of the substantially continuous wall.

15. The flexible strand according to claim **1** wherein the agent is selected from the group consisting of an anti-inflammatory, anti-coagulant, cytostatic, antibiotic, anti-neoplastic, vasodilator, anti-viral, immunosuppressive, growth factor, pro-agent, hormone, radiotherapeutic, radiopaque, peptide, protein, enzyme, or combinations thereof.

16. The flexible strand according to claim 1 wherein the strand is configured to release the agent over three years.

17. The flexible strand according to claim 1 wherein the strand is configured to release the agent in less than three years.

18. The flexible strand of claim 1, wherein the agent exerts an effect on the subject's physiology following release.

19. The flexible strand of claim 1, wherein the strand is configured to be implanted into a target tissue in the subject using one or more implantation needles.

20. A flexible, non-radioactive strand comprising a marker component and a therapeutic, prophylactic, and/or diagnostic agent, the agent, marker, or both, being imageable,

the marker component having a length extending along a centerline of the marker component between a first end and a second end and having a substantially continuous wall along the length, the substantially continuous wall bounding a hollow interior and at least partially enveloping the agent within the hollow interior, and

wherein the length of the marker component is greater than an average diameter of the hollow interior and the substantially continuous wall includes at least one opening adapted to allow the agent to pass out of the hollow interior wherein the strand do not contain a radioisotope.

21. The flexible strand according to claim 20, wherein the marker component comprises an imageable substrate and the agent is dispersed in the substrate.

22. The flexible strand according to claim 20, further comprising a substrate comprising a biodegradable material, the marker and the agent.

23. The flexible strand according to claim 20 wherein the strand is configured to release the agent over three years or less.

24. The flexible strand of claim 20, wherein the agent exerts an effect on the subject's physiology following release.

25. The flexible strand of claim 20, wherein the strand is configured to be implanted into a target tissue in the subject using one or more implantation needles.

* * * * *

EXHIBIT E

US008821835B2

(12) **United States Patent**
Kaplan

(10) **Patent No.: US 8,821,835 B2**
(45) **Date of Patent: *Sep. 2, 2014**

(54) **FLEXIBLE AND/OR ELASTIC BRACHYTHERAPY SEED OR STRAND**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/916,916**

(22) Filed: **Jun. 13, 2013**

(65) **Prior Publication Data**

US 2013/0280168 A1 Oct. 24, 2013

Related U.S. Application Data

(63) Continuation of application No. 12/823,700, filed on Jun. 25, 2010, now Pat. No. 8,470,294, which is a continuation of application No. 10/665,793, filed on Sep. 19, 2003, now Pat. No. 7,776,310, and a continuation-in-part of application No. 09/861,326, filed on May 18, 2001, now Pat. No. 6,746,661, and a continuation-in-part of application No. 09/861,196, filed on May 18, 2001, now Pat. No. 6,514,193.

(60) Provisional application No. 60/412,050, filed on Sep. 19, 2002, provisional application No. 60/249,128, filed on Nov. 16, 2000.

(51) **Int. Cl.**
A61K 51/00 (2006.01)
A61N 5/00 (2006.01)

(52) **U.S. Cl.**
USPC **424/1.25**; 424/1.11; 424/1.29; 424/1.33; 424/9.6

(58) **Field of Classification Search**
USPC 424/1.11, 1.25, 1.29, 9.4; 600/1–8; 623/1.1, 1.34, 1.38
See application file for complete search history.

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(57) **ABSTRACT**

A flexible or elastic brachytherapy strand that includes an imaging marker and/or a therapeutic, diagnostic or prophylactic agent such as a drug in a biocompatible carrier that can be delivered to a subject upon implantation into the subject through the bore of a brachytherapy implantation needle has been developed. Strands can be formed as chains or continuous arrays of seeds up to 50 centimeters or more, with or without spacer material, flaccid, rigid, or flexible.

20 Claims, 6 Drawing Sheets

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FIG. 1

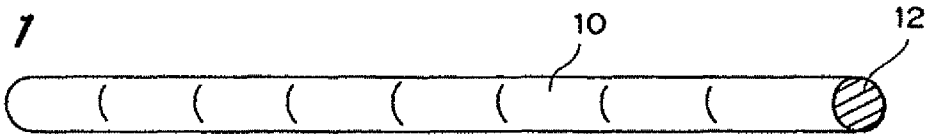


FIG. 2

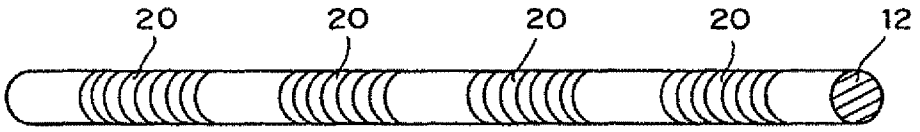


FIG. 3A

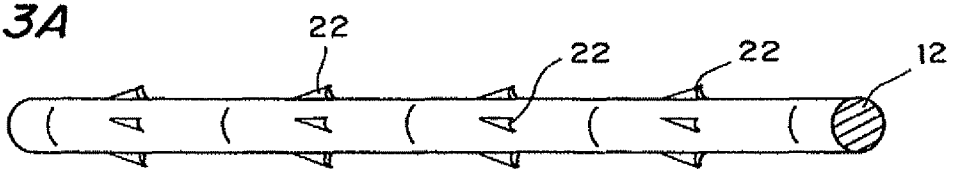


FIG. 3B

FIG. 3C

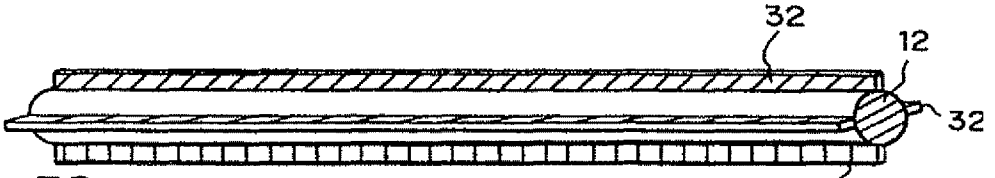


FIG. 3D

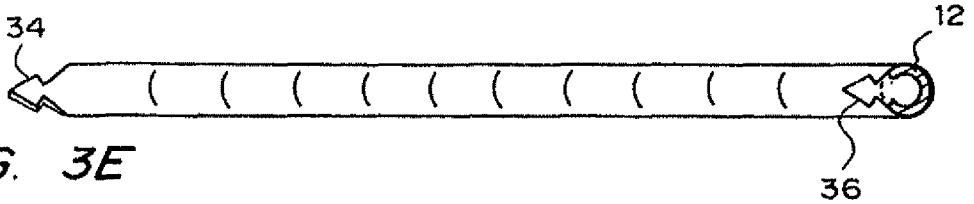
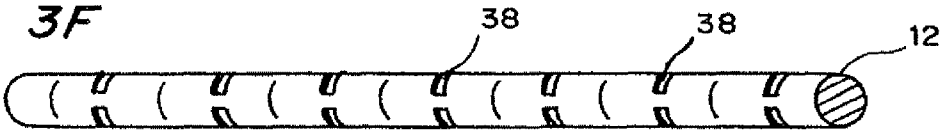


FIG. 3E

FIG. 3F



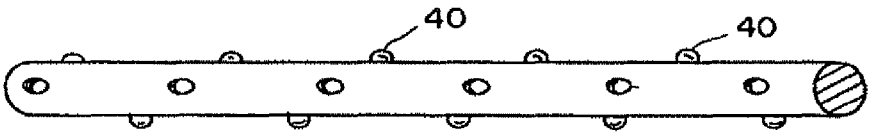


FIG. 3G

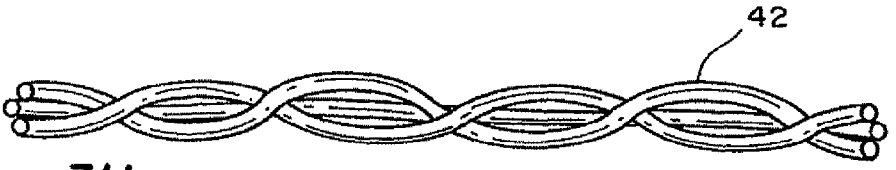


FIG. 3H

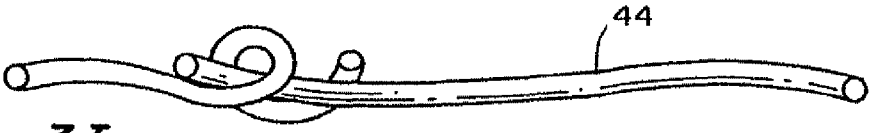


FIG. 3I

FIG. 4A

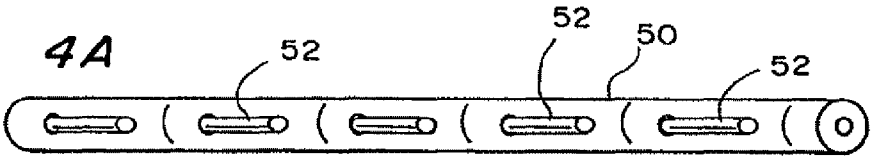


FIG. 4B

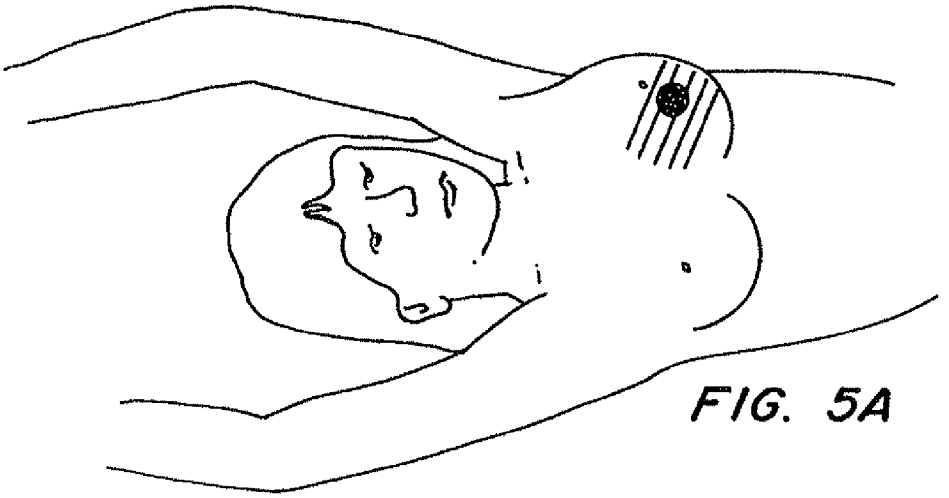


FIG. 5A

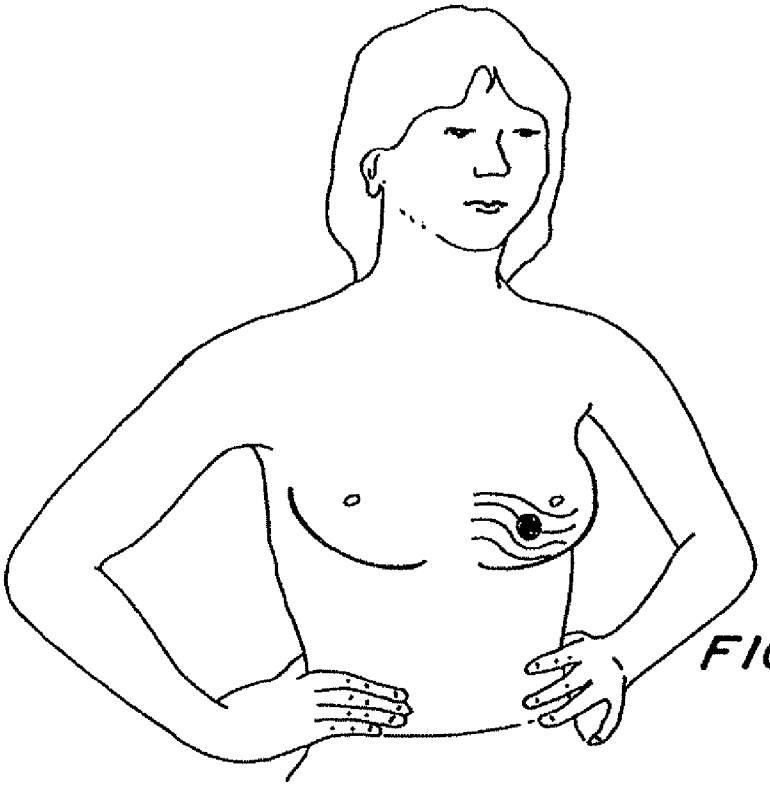


FIG. 5B

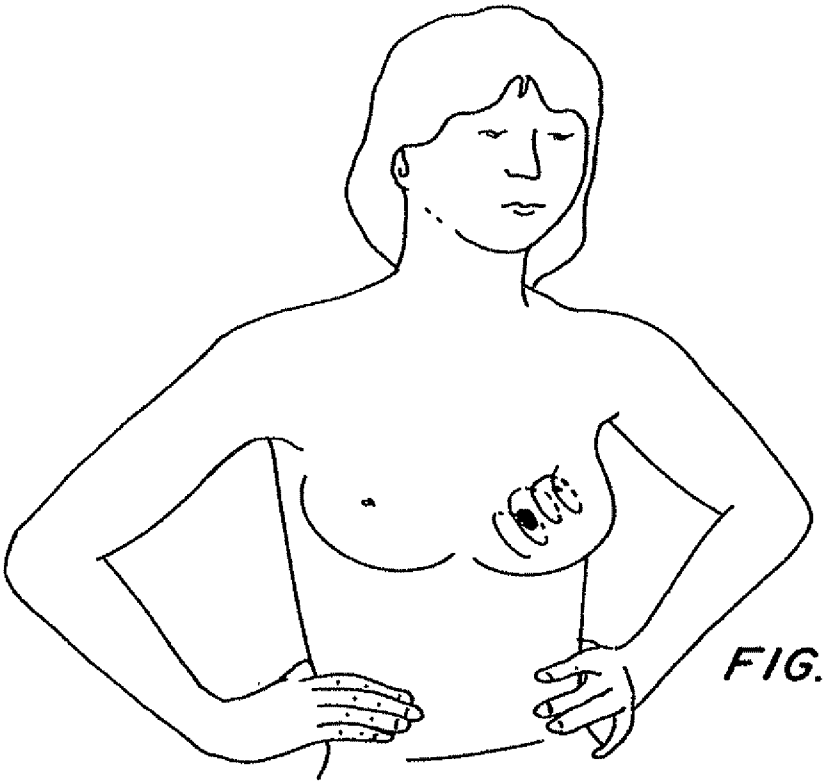


FIG. 5C

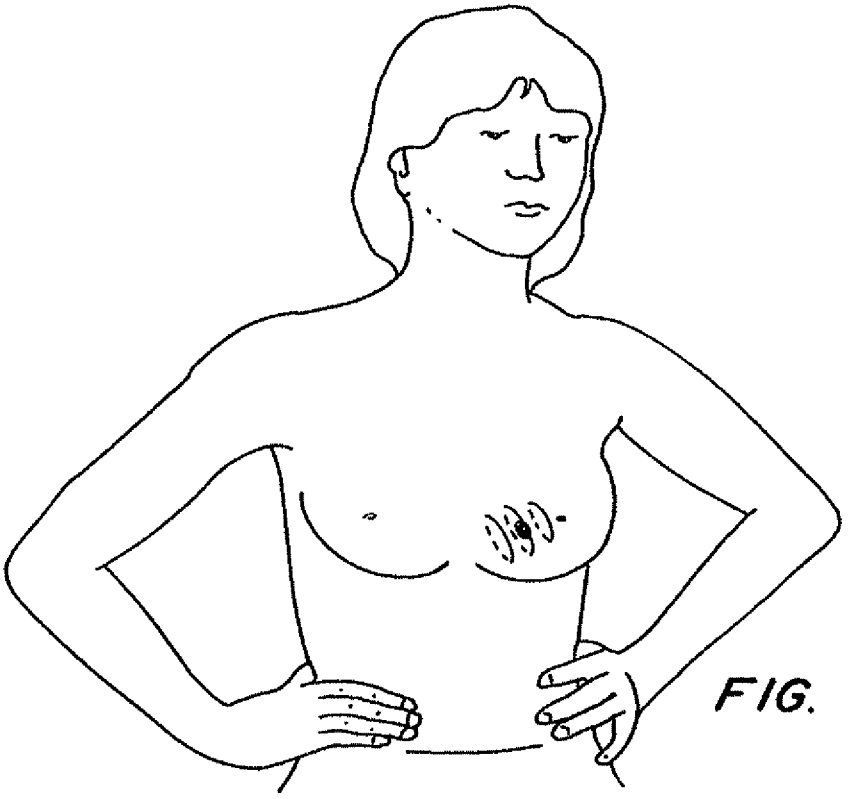
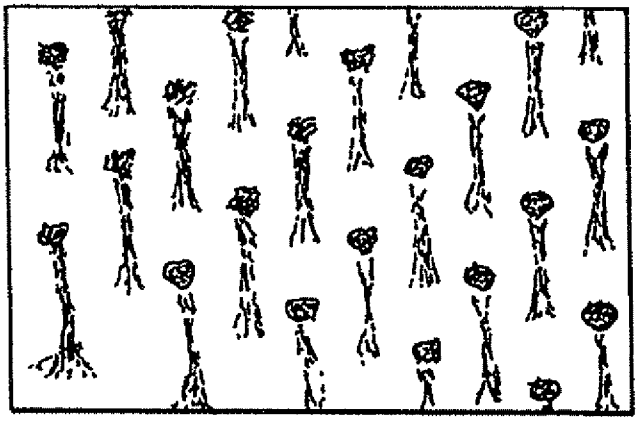


FIG. 5D

FIG. 6



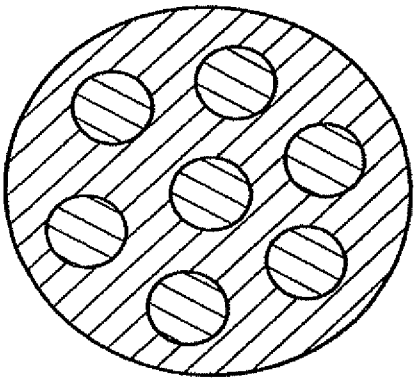


FIG. 7A

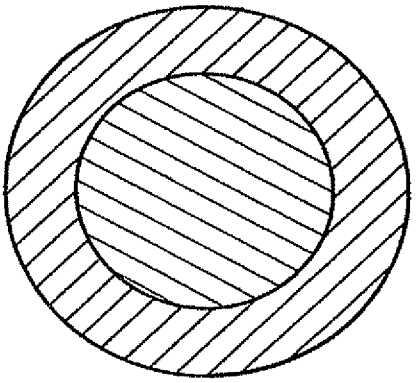


FIG. 7B

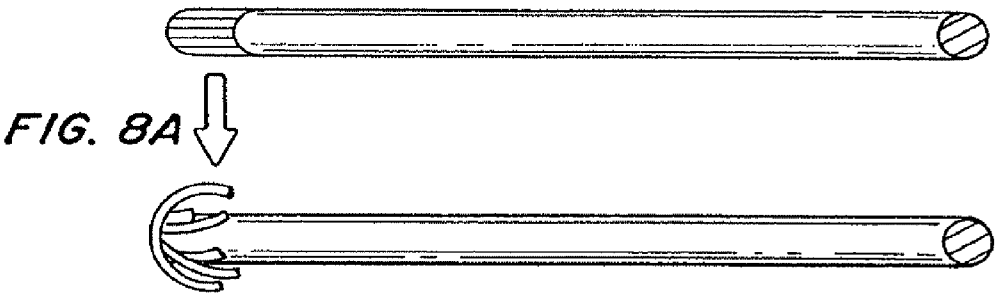


FIG. 8A

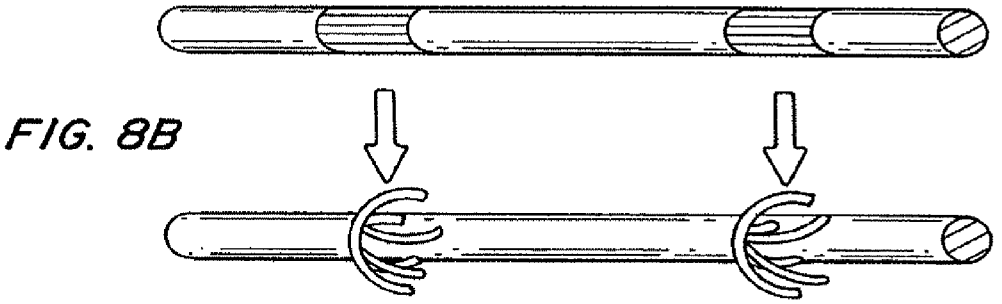


FIG. 8B

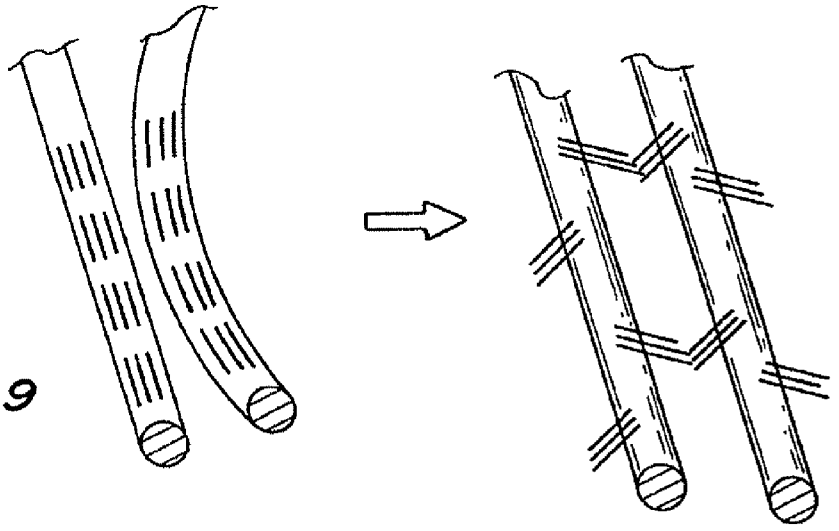


FIG. 9

FLEXIBLE AND/OR ELASTIC BRACHYTHERAPY SEED OR STRAND

The present application is a continuation of U.S. Ser. No. 12/823,700, filed Jun. 25, 2010, entitled "Flexible and/or Elastic Brachytherapy Seed or Strand", by Edward J. Kaplan, which is a continuation of U.S. Ser. No. 10/665,793, filed Sep. 19, 2003, now U.S. Pat. No. 7,776,310, issued Aug. 17, 2010, entitled "Flexible and/or Elastic Brachytherapy Seed or Strand", by Edward J. Kaplan, which claims priority to and benefit of U.S. Provisional Application No. 60/412,050, filed Sep. 19, 2002, and is a continuation-in-part of U.S. Ser. No. 09/861,326 filed May 18, 2001, now U.S. Pat. No. 6,746,661, issued Jun. 8, 2004, which claims priority to and benefit of U.S. Provisional Application 60/249,128 filed Nov. 16, 2000, and U.S. Ser. No. 10/665,793, filed Sep. 19, 2003, now U.S. Pat. No. 7,776,310, issued Aug. 17, 2010 is also a continuation-in-part of U.S. Ser. No. 09/861,196 filed May 18, 2001, now U.S. Pat. No. 6,514,193, issued Feb. 4, 2003, which claims priority to and benefit of U.S. provisional application 60/249,128 filed Nov. 16, 2000, all of which are herein incorporated in their entirety by reference.

BACKGROUND OF THE INVENTION

This application relates to imagable implantable brachytherapy devices, and methods of use thereof.

Radioactive seed therapy, commonly referred to as brachytherapy, is an established technique for treating various medical conditions, most notably prostate cancer. In a typical application of brachytherapy for treating prostate cancer, about 50-150 small seeds containing a radioisotope that emits a relatively short-acting type of radiation are surgically implanted in the diseased tissue. Because the seeds are localized near the diseased tissue, the radiation they emit is thereby concentrated on the cancerous cells and not on distantly located healthy tissue. In this respect, brachytherapy is advantageous over conventional external beam radiation.

A number of devices have been employed to implant radioactive seeds into tissues. See, e.g., U.S. Pat. No. 2,269,963 to Wappler; U.S. Pat. No. 4,402,308 to Scott; U.S. Pat. No. 5,860,909 to Mick; and U.S. Pat. No. 6,007,474 to Rydell. In a typical protocol for treating prostate cancer, an implantation device having a specialized needle is inserted through the skin between the rectum and scrotum into the prostate to deliver radioactive seeds to the prostate. The needle can be repositioned or a new needle used for other sites in the prostate where seeds are to be implanted. Typically, 20-40 needles are used to deliver between about 50-150 seeds per prostate. A rectal ultrasound probe is used to track the position of the needles. Once the end of a given needle is positioned in a desired location, a seed is forced down the bore of the needle so that it becomes lodged at that location.

As the seeds are implanted in the prostate as desired, the needles are removed from the patient. Over the ensuing several months the radiation emitted from the seeds kills the cancerous cells. Surgical removal of the seeds is usually not necessary because the type of radioisotope generally used decays over the several month period so that very little radiation is emitted from the seeds after this time. Currently marketed radioactive seeds take the form of a capsule encapsulating a radioisotope. See, e.g., Symmetra® I-125 (Bang, GmbH, Germany); IoGold™ I-125 and IoGold™ Pd-103 (North American Scientific, Inc Chatsworth, Calif.); Best® I-125 and Best® Pd-103 (Best Industries, Springfield, Va.); Brachyseed® I-125 (Draximage, Inc., Canada); Intersource®Pd-103 (International Brachytherapy, Belgium); Oncoseed® I-125 (Nycomed Amersham, UK); STM 1250 I-125 (Sourcetech Medical, Carol Stream, Ill.); Pharmaseed® I-125 (Syncor, Woodland Hills, Calif.); Prostaseed™ I-125 (Urocor, Oklahoma City, Okla.); and I-Plant® I-125 (Implant Sciences Corporation, Wakefield, Mass.). The capsule of these seeds is made of a biocompatible substance such as titanium or stainless steel, and is tightly sealed to prevent leaching of the radioisotope. The capsule is sized to fit down the bore of one of the needles used in the implantation device. Since most such needles are about 18 gauge, the capsule typically has a diameter of about 0.8 mm and a length of about 4.5 mm.

The two radioisotopes most commonly used in prostate brachytherapy seeds are iodine (I-125) and palladium (Pd-103). Both emit low energy irradiation and have half-life characteristics ideal for treating turners. For example, I-125 seeds decay at a rate of 50% every 60 days, so that at typical starting doses their radioactivity is almost exhausted after ten months. Pd-103 seeds decay even more quickly, losing half their energy every 17 days so that they are nearly inert after only 3 months.

Radioactive brachytherapy seeds may also contain other components. For example, to assist in tracking their proper placement using standard X-ray imaging techniques, seeds may contain a radiopaque marker. Markers are typically made of high atomic number (i.e. "high Z") elements or alloys or mixtures containing such elements. Examples of these include platinum, iridium, rhenium, gold, tantalum, lead, bismuth alloys, indium alloys, solder or other alloys with low melting points, tungsten, and silver. Many radiopaque markers are currently being marketed. Examples include platinum/iridium markers (Draximage, Inc. and International Brachytherapy), gold rods (Bebig GmbH), gold/copper alloy markers (North American Scientific), palladium rods (Syncor), tungsten markers (Best Industries), silver rods (Nycomed Amersham), silver spheres (International Isotopes Inc. and Urocor), and silver wire (Implant Sciences Corp.). Other radiopaque markers include polymers impregnated with various substances (see, e.g., U.S. Pat. No. 6,077,880).

A number of different U.S. patents disclose technology relating to brachytherapy. For example, U.S. Pat. No. 3,351,049 to Lawrence discloses the use of a low-energy X-ray-emitting, interstitial implant as a brachytherapy source. In addition, U.S. Pat. No. 4,323,055 to Kubiatowicz; U.S. Pat. No. 4,702,228 to Russell; U.S. Pat. No. 4,891,165 to Suthanthiran 5,405,309 to Carden; U.S. Pat. No. 5,713,828 to Coniglione U.S. Pat. No. 5,997,463 to Cutrer; U.S. Pat. No. 6,066,083 to Slater; and U.S. Pat. No. 6,074,337 to Tucker disclose technologies relating to brachytherapy devices.

The seeds have also been utilized to treat other types of cancers, such as pancreas, liver, lung and brain. For technical reasons, other organ systems or tissues are not amenable to this type of permanent seed implantation. These include hollow viscera such as the urinary bladder, mobile/muscular viscera such as the base of tongue, and tissues where a cavity or tumor bed has been created as a result of resection, as in the breast. In hollow viscera, loose seeds cannot be reliably spaced out owing to a dearth of tissue and the associated risk of losing the seeds into the lumen or cavity of the organ. Likewise in mobile/muscular and irregularly shaped viscera such as the base of tongue, loose seeds cannot be spaced reliably, and strands of permanent seeds like those described in U.S. Pat. No. 4,354,745 to Horowitz or U.S. Pat. No. 5,322,499 to Liprie are still too inflexible to be used because of the metallic seeds that are embedded within them. Similarly, the wire coils described in U.S. Pat. No. 6,436,026 to

Sioshansi, although flexible, are not meant to be implanted permanently and require a means of afterloading and removal.

The situation in breast cancer is similar to that of a hollow organ, whereby loose seeds are difficult to space properly, and may fall into the resection cavity, thus spoiling the dosimetry plan. Despite U.S. Patent application No. 20020087078 by Cox which describes the insertion of a radioactive seed into a breast with cancer, the seed is placed inside the actual breast cancer and is removed along with the tumor at the time of the cancer surgery. Therefore, in this instance, the radioactive seed is not meant to serve a therapeutic purpose. Breast tissue is also similar to the base of tongue or other mobile organs since the breast may be very generous and supple, conforming to forces of gravity or pressure. In fact, for these reasons, metallic seeds are not currently used for permanent therapeutic implantation into a breast.

In each of the above circumstances where use of permanent seeds is not desirable, temporary implants are generally used. This is accomplished via placement of afterloading devices such as the Henschke applicator for cervix cancer, hairpin needles for the base of tongue, and silastic catheters for breast cancer. Once the respective applicators have been placed, radioactive sources are loaded and remain indwelling for a prescribed finite period, usually hours to days. The sources and afterloading devices are then completely removed.

Disadvantages of these temporary systems are that patients often must stay in the hospital for the cadre time that low dose rate sources are indwelling, or between radiotherapy fractions or sessions if high dose rate sources are used. In the case of afterloading catheters, the catheters are sutured in place for several days, causing acute pain, swelling, and possible infection or scarring. In the case of base of tongue implants, patients frequently require temporary tracheostomies to keep their airway open while the hairpin needles remain in place. In one new temporary high dose rate system by Proxima Therapeutics®, surgical placement of a balloon catheter is performed on the breast. The device has a catheter leading from the balloon in the tumor bed to the skin to provide ingress and egress for the temporary brachytherapy source. The balloon is deflated at the conclusion of several days of brachytherapy sessions, and is pulled out of the breast by hand.

It is an object of the present invention to provide biodegradable strands or other structures that are flexible and permanently implantable.

It is another object of the present invention to provide biodegradable strands or other structures that are flexible and implantable.

It is still another object of the present invention to provide non polymeric biodegradable implantable seeds and a means for readily imaging implanted seeds.

It is also an object of the present invention to provide brachytherapy seeds and strands which can be used for ether purposes, for example, drug delivery.

SUMMARY OF THE INVENTION

A brachytherapy strand that is elastic and/or flexible and preferably biodegradable has been developed. A drug or other therapeutically active substance or diagnostic can be included in the strand in addition to, or as an alternative to, a radioisotope. The rate of release in the implantation site can be controlled by controlling the rate of degradation and/or release at the implantation site, in the preferred embodiment, the strands also contain a radioopaque material or other means for external imaging. The flexible material may be polymeric or inorganic material. Strands can be formed as chains or continuous arrays of seeds up to 50 centimeters or more, with or without spacer material, flaccid, rigid, or flexible.

Like conventional radioactive brachytherapy seeds, the strands can be precisely implanted in many different target tissues without the need for invasive surgery. In the preferred embodiment, the strands are implanted into the subject through the bore of a brachytherapy implantation needle or catheter. The therapeutically active substance included within a strand can be delivered in a controlled fashion over a relatively long period of time (e.g., weeks, months, or longer periods). Since concentrations of the therapeutically active substance will be greater at the implantation sue (e.g., the diseased tissue), any potential deleterious effect of the therapeutically active substance on healthy tissue located away from the implantation site will be reduced.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic side view of a cylindrically shaped brachytherapy strand.

FIG. **2** is a schematic side view of a hollow tube-shaped brachytherapy strand.

FIGS. **3**A-**3**I are strands with inert spacers, interspersed for cutting (FIG. **3**A); with pop-up wings to prevent migration or shifting after implanting (FIG. **3**B); with a radiopaque strip running through it (FIG. **3**C); with cross-style stabilizers (FIG. **3**M with male and female ends to facilitate joining, e.g., in a ring (FIG. **3**E); with indentations for cutting or breaking into smaller strands (FIG. **3**F); with a stabilizer, such as bumps (FIG. **3**G); a braided strand (FIG. **3**H); and strands knotted together (FIG. **3**I).

FIGS. **4**A and **4**B are a strand with radioactive seeds interspersed (perspective view, FIG. **4**A cross-sectional view, FIG. **4**B).

FIGS. **5**A-**5**D are perspective views of strands after introduction into breast adjacent to lumpectomy site (larger circle) below the nipple (smaller circle) (FIG. **5**A); strands conforming to shape of breast with patient now upright, lumpectomy site is shown as larger black circle, nipple as smaller circle (FIG. **5**B); strand deployed as a coil (FIG. **5**C) and strands deployed as rings around lumpectomy site (FIG. **5**D).

FIG. **6** is a depiction of microfabricated polyimide hairs used as a coating for the brachytherapy seed or strand to impart adhesive properties.

FIGS. **7**A and **7**B are transverse cross-section views of a brachytherapy strand with multiple internal conduits (FIG. **7**A) or a single conduit (FIG. **7**B).

FIGS. **8**A and **8**B are depictions of a brachytherapy strand equipped with shape memory polymeric anchoring structures at the ends of the strand (FIG. **8**A) and interspersed along the length of the strand (FIG. **8**B), before and after deployment.

FIG. **9** is a depiction of a brachytherapy strand equipped with shape memory polymeric anchors positioned to brace or center the strands within irregularly shaped tissues.

DETAILED DESCRIPTION OF THE INVENTION

An elastic and/or flexible, and preferably biodegradable, brachytherapy seed or strand of seeds, has been developed. As used herein "elastic" refers to a material which has the ability to recover from relatively large deformations, or withstand them, or which can be elongated to multiple times its original length, without breaking. In one preferred embodiment, the brachytherapy strand includes a biocompatible component, a therapeutically active component that includes a non-radioactive drug, and in a more preferred embodiment, a radio-

paque marker. The biocompatible component is physically associated with a therapeutically active component and in contact with the marker. In a second embodiment, the brachytherapy strand includes a non-metal biocompatible component, a therapeutically active component comprising a radioisotope, and a radiopaque or other diagnostic marker, the biocompatible component being (a) physically associated with a therapeutically active component and (b) in contact with the diagnostic marker, wherein the brachytherapy strand has a size and shape suitable for passing through the bore of a needle typically having an interior diameter of less than about 2.7 millimeters (10 gauge), in another embodiment, the biocompatible component is biodegradable.

Depending on the particular application, the brachytherapy strands offer other advantages. Among these, for example, compared to conventional systemic administration (e.g., oral or intravenous delivery) of therapeutically active substances, the brachytherapy strands can provide higher and more consistent concentrations of a therapeutically active substance to a target tissue. They can also eliminate the need for repeated injections as well as circumvent delivery problems such as where a target tissue lacks an intact vascular supply (e.g., a target tissue whose blood flow may be compromised) or is otherwise sequestered from the blood supply (e.g., via the blood-brain barrier of the central nervous system). In some embodiments of the strands that do not contain a radioisotope (e.g., those having only the therapeutically active substance and biodegradable component), after the therapeutically active substance is completely released and the biodegradable component is fully decomposed, no foreign device will remain at the implantation site.

I. Brachytherapy Strands

Brachytherapy strands typically have a size and shape suitable for passing through the bore of a needle having an interior diameter of less than about 23 millimeters (10 gauge), less than about 1.4 millimeters (15 gauge), less than about 0.84 millimeters (18 gauge), or less than about 0.56 millimeters (24 gauge). In one version, the strand is shaped into a cylinder having a diameter of between about 0.5 to 3 millimeters and a length of 20, 30, 40 centimeters or more.

A. Materials for Making the Brachytherapy Seeds

Any appropriate biocompatible material can be used to form the brachytherapy seeds. Preferred materials include polymeric materials which are approved by the Food and Drug Administration for implantation.

In the preferred embodiment, the seeds are formed of a biodegradable material. Examples of suitable materials include synthetic polymers such as polyhydroxyacids (polylactic acid, polyglycolic-lactic acid), polyanhydrides (poly (bis(p-carboxyphenoxy) propane anhydride, poly(bis(p-carboxy) methane anhydride), copolymer of poly carboxyphenoxypropane and sebacic acid); polyorthoesters; polyhydroxyalkanoates (polyhydroxybutyric acid); and poly (isobutylcyanoacrylate). Other examples include open cell polylactic acid; co-polymers of a fatty acid dimer and sebacic acid; poly(carboxyphenoxy) hexane; poly-1,4-phenylene dipropionic add; polyisophthalic acid; polydodecanedioic acid; poly(glycol-sebacate) (PGS); or other polymers described below. See, e.g., Biomaterials Engineering and Devices: Human Applications: Fundamentals and Vascular and Carrier Applications, Donald L. Wise et al. (eds), Humana Press, 2000; *Biomaterials Science: An Introduction to Materials in Medicine*, Buddy D. Ratner et al. (eds.), Academic Press, 1997; and *Biomaterials and Bioengineering Handbook*, Donald L. Wise, Marcel Dekker, 2000.

These polymers can be obtained from sources such as Sigma Chemical Co., St, Louis, Mo.; Polysciences, Warrenton, Pa.; Aldrich, Milwaukee, Wis.; Fluke, Ronkonkoma, N.Y.; and BioRad, Richmond, Calif., or can be synthesized from monomers obtained from these or other suppliers using standard techniques.

In addition to synthetic polymers, natural polymers may also be used. In the preferred embodiment, the natural polymers are biodegradable. For example, tissue such as connective tissue from the walls of blood vessels or extracellular matrix may be used as a biodegradable carrier for delivery of radiation or another therapeutic substance. Set, for example, U.S. Pat. No. 5,429,634 to Narcisco. Tissue may be autologous, heterologous, engineered, or otherwise modified so long as it is biocompatible with the target tissue. A patient may donate his own tissue to serve as a carrier for the therapeutic substance and/or radionuclide. Other tissues or natural polymers may serve as the degradable carrier matrices. For example, polysaccharides such as starch and dextran, proteins such as collagen, fibrin (Perks, et al., Tissue Eng. 7:359-361 (2001) and Senderoff, et al., J. Parenteral 45:2-6 (1991)), and albumin (see, for example, U.S. Pat. No. 5,707,644 to Ilum), elastin-like peptides, lipids, and combinations thereof. These materials can be derived from any of the sources known to those skilled in the art, including the patient's own tissues or blood.

Seeds or strands can also be made from synthetic or natural biocompatible non-polymeric and/or inorganic materials, which are preferably biodegradable. See for example, WO 99/53898 describing bioabsorbable porous silicon seeds and WO 00/50349 describing biodegradable ceramic fibers from silica sols. Other examples of non-polymeric and/or organic materials include: U.S. Pat. No. 5,640,705 to Koruga describing radiation-containing fullerene molecules; WO 02/34959A2 by Yeda Research and Development Co, Ltd. describing inorganic fullerene-like nanoparticles or structures; EP 1205437A1 to Osawa describing nano-size particulate graphite and multi-layer fullerene; U.S. Pat. No. 5,766,618 to Laurencin describing a polymeric-hydroxyapatite bone composite; GB 235140A to Asako Matsushima describing a ceramic composite such as hydroxyapatite for sustained release; and U.S. Pat. No. 5,762,950 to Antti Yli-Urpo disclosing a calcium phosphate, e.g. hydroxyapatite, bioactive ceramic for timed release.

In the case of radioactive seeds, it can be left to the clinician to select from any number of biodegradable carrier matrices which contain the radionuclide, so king as the degradation characteristics of the carrier substance are consistent with the desired absorption profile. This is because the carrier matrix itself will be sequestered from the surrounding target tissue along with the radionuclide until the radionuclide has decayed to an insignificant activity. At that time or afterwards, the biodegradable layer overlying the radioactive matrix will be eroded away, thus beginning is similar process for the now non-radioactive or nearly spent radioactive carrier.

Strands may also be made of non-biodegradable materials, especially the radioopaque strand materials currently used to form beads for treatment of prostate cancer, although this is not as preferred as the biodegradable materials. As described above, the capsule (and as described herein, the strand) of these seeds is made of a biocompatible substance such as titanium or stainless steel, which is tightly sealed to prevent leaching of the radioisotope.

B. Radioactive Tracers

Optionally, brachytherapy seed or strand can be imparted with a means of tracing the radioactive contents should those contents be released inadvertently. Unforeseen problems associated with leakage of radioactive material, whether it be into the surrounding tissues in a patient, in a pathology lab, in

a nuclear medicine lab, or in the operating room have been recently discovered as they relate to polymer seeds. The seed/strand should contain a means of tracing their contents should those contents be released inadvertently. This mechanism can rely on inclusion of fluorescent, luminescent, colored, pigmented or other approaches for tagging, detecting, or otherwise identifying the seed/strand contents either visually or with instrument assistance.

Fluorescence can be imparted using the appropriate polymer or other biodegradable substance, such as described by Sung in U.S. Pat. No. 4,885,254, Bryan in U.S. Pat. No. 6,416,960 B1. Barbera-Guillem in U.S. Pat. No. 6,548,171 B1, or Greiner in U.S. Patent Application No. 2003/0010508A1.

Luminescence can be imparted using the appropriate polymer or other biodegradable substance, such as described by Towns in WO01/49768 A2, Sakakibara in EP 1 311 138 A1, Bryan in U.S. Pat. No. 6,436,682B1, Hancock in U.S. Patent Application No. 2003/0134959A1, or Wood in U.S. Pat. No. 6,552,179B1. Bioluminescence materials are described in U.S. Pat. No. 5,670,356. In addition, chemiluminescent and electro luminescent substances might be utilized, as we as other types of luminescent substances as would be known to one skilled in the art.

Quantum dots may also be loaded into the seeds and utilized to locate spilled substances from ruptured seeds/strands, like those described in U.S. Patent Application No. 2003/0129311A1 or Dobson in WO 95/13891 (see also Jaiswal et al., *Nature Biotechnology* 2003; 21:47-51, and Quantum Dot Corporation's Qdot™ biotin conjugate).

Dyed biodegradable polymeric material may be used, as described by Burkhard in EP 1 093 824 A2. Other dyes can be used as indicated. Ultraviolet light can be utilized to detect a therapeutic agent like radioactive substances or drugs using a format described by Koshihara in U.S. Pat. No. 6,456,636 B1, or by Nakashima in WO 00/53659. Infrared dyes may be used, as described by Paulus in U.S. Pat. No. 5,426,143.

Those skilled in the art will be familiar with labeling, doping, or tagging the contents of the seeds/strands with agents that can be identified without modification, or pro-agents that can be identified by the addition of an activating substance or other means, such as labeled antibodies and the like.

C. Therapeutic and Diagnostic Agents

Polymers can be used to form, or to coat, drug delivery devices such as strands or strands containing any of a wide range of therapeutic and diagnostic agents. Any of a wide range of therapeutic, diagnostic and prophylactic materials can be incorporated into the strands, including organic compounds, inorganic compounds, proteins, polysaccharides, and nucleic acids, such as DNA, using standard techniques.

The non-radioactive drug can take the form of stimulating and growth factors; gene vectors; viral vectors; anti-angiogenesis agents; cytostatic, cytotoxic, and cytocidal agents; transforming agents; apoptosis-inducing agents; radiosensitizers; radioprotectants; hormones; enzymes; antibiotics; antiviral agents; mitogens; cytokines; anti-inflammatory agents; immunotoxins; antibodies; or antigens. For example, the non-radioactive therapeutic can be an anti-neoplastic agent such as paclitaxel, 5-fluorouracil, or cisplatin. It can also be a radiosensitizing agent such as 5—fluorouracil, etanidazole, tirapazamine, bromodeoxyuridine (BUdR) and iododeoxyuridine (IUdR).

Many different therapeutically active substances have been associated with biocompatible materials for use in drug delivery systems apart from brachytherapy strands. These include, for example, adriamycin (Moritera et al., *Invest. Ophthal. Vis. Sci.* 33:3125-30, 1992); bupivicaine (Park et al., *J. Controlled Release* 52:179-189, 1998); camptothecin (Weingart et al., *Int. J. Cancer* 62:1-5, 1995); carboplatin. (Chen et al., *Drug Delivery* 4:301-11, 1997); carmustine (Brem et al., *J. Neurosnrg* 74:441-6, 1991; and U.S. Pat. Nos. 4,789,724 and 5,179,189); cefazolin (Park et al., *J. Controlled Rel.,* 52:179-189, 1998); cisplatin (Yapp et al., *IJROBP* 39:497-504, 1997); cortisone (Tamargo et al., *Neurooncol.* 9:131-8, 1990); cyclosporine (Sanchez et al., *Drug Delivery* 2:21-8, 1995); daunorubicin (Dash et al., *J. Pharmacol. Tox. Meth.* 40:1-12, 1999); dexamethasone (Reinhard et al., *J. Contr. Ret,* 16:331-340, 1991); dopamine (During et al., *Ann. Neurol,* 25:351-6, 1989); etanidazole (Yapp et al., *Radiotherapy Oncol.* 53:77-84, 1999); 5-fluorouracil (Menei et al., *Cancer* 86:325-30, 1999); fluconazole (Miyamoto et al., *Curr. Eye Res.* 10:930-5, 1997); 4-hydroxycyclophosphamide (Judy et al., *J. Neurosurg.* 82:481-6, 19 ganciclovir (Kunou et al., *Controlled. Rel.* 37:143-150, 1995); gentamicin (Laurentin et al., *J. Orthopaed. Res.* 11:256-62, 1993); heparin (Tamargo et al., *J. Neurooncol.* 9:131-8, 1990); interleukin-2 (Kuriakose et al., *Head & Neck* 22:57-63, 2000); naproxen (Conforti et al., *J. Pharm Pharmacol.* 48:468-73, 1996); nerve growth factor (Camerata et al., *Neurosurgery* 30:313-19, 1992); retroviral vector producer cells to transfer a cytotoxic gene product (Beer et al., *Adv. Drug Deliver. Rev.* 27:59-66, 1997); taxol (Park et al., *J. Controlled Rel.* 1998; and Harper, E et al., *Clin. Cancer Res.,* 5:4242-4248, 1999); tetanus toxoid (Alonso et al., *Vaccine* 12:299-306, 1994); tetracaine hydrochloride (Ramirez et al., *J. Microencap.* 16:105-15, 1999); tirapazamine (Yuan et al., *Radiation Oncol. Investig.* 7:218-30, 1999); thyrotropin-releasing hormone (Kubek et al., *Brain Rel.* 809: 189-97, 1998); and vaccines (Chattaraj et al., *J. Controlled Rel.* 58:223-32, 1999). Other therapeutically active substances that can be combined with a biocompatible component include: anesthetics, angiogenesis inhibitors (e.g., Lau D. H. et al., *Cancer Biother. Radiopharm.* 14:31-6, 1999), antibiotics (e.g., Bahk J. Y. et al., *J. Urol.* 163:1560-4, 2000; and Miyamoto H. et al., *Current Eye Research* 16:930-5, 1997), antibodies (e.g., Gomez S. M. et al., *Biotechnol. Prog.* 15:238-44, 1999), anticoagulants (e.g., Tamargo R. J. et al., J. Neurooncol, 9:131-138, 1990), antigens (e.g., Machluf M. et al., J. Pharm. Sol. 89:1550-57, 2000), anti-inflammatory agents (e.g., Reinhard C. S. et al., J. Controlled Release 16:331-40, 1991; and Tamargo R. J. et al., J. Nearosurg, 74; 956-61, 1991), antivirals, apoptosis-inhibiting agents (e.g., Macias D, et al Anat. Embryol. (Berl) 193:533-41, 1996), cytokines (e.g., Edelman E. R. et al., Biomaterials 12:619-26, 1991), cytotoxic agents (e.g., Brem H. et al., J. Neurosurg, 80:283-90, 1994; Brem H. et al., J. Neurosurg. 80:283-90, 1994; Brem H. et al., Lancet 345:1008-12, 1995; Ewend M. O. et al., Cancer Res. 56:5217-23, 1996; Prang L. K. et al., Cancer Res. 58:672-85, 1998; Grossman S. et al., J. Neurosurg, 76:640-47, 1992; Kong Q. et al., Surgical Oncology 69:76-82, 1998; Shikani A. H. et al., Laryngoscope 110:907-1.7, 2000; Straw R. C. et al., J. Orthop. Res. 12:871-7, 1994; Tamargo R. J. et al., Cancer Research 53:329-33, 1993; Valtonen S. et al., Neurosurgery 41:44-9, 1997; Waiter K. A. et al., Cancer Research 54:2207-12, 1994; Yapp D. T. T. et al., IJROBP 39:497-504, 1997; Yapp D. T. T.: et al., Anti-Cancer Drugs 9:791-796, 1998; Yapp D. T. T. et al. IJROBP 42:413-20, 1998; and Yoshida M. et al., Biomaterials 10:16-22, 1989), enzymes (e.g., Park T. G. et al., J. Control Release 55:181-91, 1998), gene vectors (e.g., Hao T. et al., J. Control Release 69:249-59, 2000; and Maheshwari A. et al., Mol Ther, 2:121-30, 2000), hormones (e.g., Rosa D. et al., J. Control Release 69:283-95, 2000), immunosuppressants (e.g., Sanchez A. et al., Drug Delivery 2:21-8, 1995), mito-

gens (e.g., Ertl B. et al., J. Drug Target 8:173-84, 2000), neurotransmitters (e.g., During M. J. et al., Ann Neurology 25:351-6, 1989), radioprotectants Monig H, et al., Strahlenther Onkol. 166:235-41, 1990), radiosensitizers (e.g., Williams J. A. et al., IJROBP 42:631-1998; and Cardinale R. M., et al., Radiat. Oncol. Invest. 6:63-70, 1998), stimulating and growth factors, transforming agents (e.g., Hong L. et al., Tissue Eng. 6:331-40, 2000), and viral vectors.

Various known methods and seeds relate to the application of heat to a target tissue for the purpose of killing cancerous cells (see for example Gordon in U.S. Pat. No. 4,569,836 and Delannoy in U.S. Pat. No. 5,284,144). Prior art metallic seeds known as "thermoseeds" have been described by Paulus in U.S. Pat. No. 5,429,583. In contrast to metal thermoseeds that generate heat mainly by eddy current loss, ferromagnetic microspheres generate heat predominantly by hysteresis loss.

Since it is widely known that clinically relevant heating of tissues can be generated by magnetic hysteresis effects, a preferred embodiment includes a magnetically imbued biodegradable carrier within the strands/seeds. Widder described an intravascular version of this kind of ferromagnetic microsphere in U.S. Pat. No. 4,247,406. Mitsamori et al. used a dextran-magnetite degradable starch microsphere in their work on inductive hyperthermia in rabbits (Mitsumori et al. *Int J Hyperthermia* 1994; 10:785-93) Minamimura et al. were the first investigator to show significant anti-tumor efficacy in turn bearing rats who were injected with dextran-magnetite microspheres that were then exposed to magnetic forces to generate heat within the tumors (Minamimura et al., *Int. J. Oncol.* 2000; 16:1153-8). Moroz et al. described successful beating of deep-seated soft tissue in pigs above the critical 42° C. therapeutic threshold following infusions of magnetic iron oxide-doped polymer microspheres (Moroz et al., J. Surg. Res. 2002; 105:209-14).

In addition to polymers and starch, other biodegradable substrates can be incorporated into the seeds described herein, as desired by those skilled in the art. Viroonchatapan et al. used thermosensitive dextran-magnetite magnetoliposomes in their in vitro experiments (Viroonchatapan et al, *Pharm. Res.* 1995; 12:1176-83), while Arcos et al. described a new type of biphasic magnetic glass-ceramic mixed with sol-gel glass that has the capability to act as thermoseeds (Arcos et al., *J. Biomed. Mater. Res.* 2003; 65A71-8).

The claimed brachytherapy seed or strand may also be used for local cancer therapy. In a preferred embodiment, oxygen, hemoglobin, synthetic hemoglobin-like substances, and drugs that enhance tissue oxygen perfusion are included in the biodegradable substrate. Iwashita described a polymer oxygen carrier in U.S. Pat. No. 4,412,989. Bonaventura described a polymeric hemoglobin carrier in U.S. Pat. No. 4,343,715, and Chang described a biodegradable polymer containing hemoglobin in U.S. Pat. No. 5,670,173. Kakizaki et al. reported on a lipidheme synthetic microspheric oxygen carrier that released oxygen in tissue in vivo (*Artif Cells. Blood Substit. Immobil. Biotechnol.* 1994; 22:933-8). Bobofchak et al. recently published their work on a recombinant polymeric hemoglobin designated Hb Minotaur (*Am. J. Physiol. Heart. Circ. Physiol.* 2003; 285:H549-61). Substances that can increase oxygen tension in tissue, include but are not limited to oxygen, L-arginine, papaverine, pentoxifylline, nicotinamide, and nitric oxide and various vasodilators.

Diagnostic compounds can be magnetic (detectable by MRI), radiopaque (detectable by x-ray), fluorescent (detectable by fluorescent techniques) or ultrasound detectable. These materials are commercially available, as are the systems for detection and measurements.

Radiopaque marker **30** can be made of any substance that can be detected by conventional X-ray imaging techniques. See, e.g., *Fundamentals of Diagnostic Radiology,* 2d ed., William E. Brant and Clyde A. Helms (eds.), Lippincott, Williams and Wilkins, 1999; *Physical Principles of Medical Imaging,* 2d ed., Perry Jr. Sprawls, Medical Physic Publishing, 1995; *Elements of Modern X-ray Physics*, Jens Als-Nielsen and Des McMorrow, Wiley & Sons, 2001; *X-ray and Neutron Reflectivity: Principles and Applications*, J. Daillant et al., Springer-Verlag, 1999; *Methods of X-ray and Neutron Scattering in Polymer Science*, Ryoong-Joon J. Roe, Oxford University Press, 2000; and *Principles of Radiographic Imaging: An Art & A Science*, Richard R. Carlton, Delmar Publishers, 2000. Many such substances that can be used as marker **30** are known including, most notably, high atomic number (i.e., "high Z") elements or alloys or mixtures containing such elements. Examples of these include platinum, iridium, rhenium, gold, tantalum, bismuth alloys, indium alloys, solder or other alloys, tungsten and silver. Many currently used radiopaque markers that might be adapted for use in the seeds described herein include platinum/iridium markers from Draximage, Inc. and International Brachytherapy; gold rods from Bebig GmbH; gold/copper alloy markers from North American Scientific, palladium rods from Syncor, tungsten markers from Best industries; silver rods from Nycomed Amersham; silver spheres from International Isotopes Inc. and Urocor; and silver wire from Implant Sciences Corp. Other radiopaque markers include polymers impregnated with various substances (see, e.g., U.S. Pat. Nos. 6,077,880; 6,077,880; and 5,746,998). Radiopaque polymers are described in European Patent Application 894, 503 filed May 8, 1997; European Patent Application 1,016,423 filed Dec. 29, 1999; and published PCT application WO 96/05872 filed Aug. 21, 1995. Those radiopaque polymers that are biodegradable are preferred in applications where it is desired to have the implant degrade over time in the implantation site.

Examples of radiopaque markers include platinum, iridium, rhenium, gold, tantalum, bismuth, indium, tungsten, silver, or a radiopaque polymer. Suitable radioisotopes include ^{125}I and ^{103}Pd.

Sometimes combinations of agents may provide enhanced results. For example, in preferred embodiment, a radiosensitizing agent such as 5-FU, etanidazole, tirapazamine, or BUdR, can be used in combination with IUdR. Various combinations of substances are known to be more effective when used in combination than when used alone. See, e.g., Brem et al., *J. Neurosurg.* 80:283-290, 1994; Ewend et al., *Cancer Res.* 56:5217-5223, 1996; Cardinale, *Radiation Oncol. Investig.* 6:63-70, Yapp et al., *Radiotherapy and Oncol.* 53:77-84, 1999; Yapp, *IJROBP* 39:497-504, 1997; Yuan et al., *Radiation Oncol, Investig.* 7:218-230, 1999; and Menei et al., *Cancer* 86:325-130, 1999.

In addition to the biodegradable radiopaque market in the seeds/strands, microbubbles may also be incorporated to facilitate ultrasonic detection. Micrometer-sized bubbles are known to be extremely potent scatterers of diagnostic frequencies, as reported by Hilgenfeldt et al. in *Ultrasonics* 2000; 38:99-104. Microbubble manufacturing is outlined by Schutt in U.S. Pat. No. 6,280,704 B1 and Schneider in U.S. Pat. No. 6,485,705 B1. The biodegradable microbubble substrate may be disposed within the seed or strand or on any or all of the outer aspect of the invention.

II. Formation of Polymeric Seeds

Although described in this application with especial reference to the formation of polymeric strands, it is understood that the same or similar technology can be used to make strands of the inorganic materials referenced above.

In one embodiment, polylactic acid strands can be fabricated using methods including solvent evaporation, hot-melt microencapsulation and spray drying. Polyanhydrides made of bis-carboxyphenoxypropane and sebacic acid or poly(fumaric-co-sebacic) can be prepared by hot-nick microencapsulation. Polystyrene strands can be prepared by solvent evaporation. Hydrogel strands can be prepared by dripping a polymer solution, such as alginate, chitosan, alginate/polyethylenimine (PEI) and carboxymethyl cellulose (CMC), from a reservoir though microdroplet forming device into a stirred ionic bath, as disclosed in WO 93/21906.

One or more diagnostic, therapeutic or prophylactic compound can be incorporated into the polymeric strands either before or after formation.

Solvent Evaporation

Methods for forming strands using solvent evaporation techniques are described in E. Mathiowitz et al., *J. Scanning Microscopy,* 4:329 (1990); L. R. Beck et al., *Fertil. Steril.* 31:545 (1979); and S. Benita et al., *J. Pharm. Sci.,* 73:1721 (1984). The polymer is dissolved in a volatile organic solvent, such as methylene chloride. A substance to be incorporated is added to the solution, and the mixture is suspended in an aqueous solution that contains a surface active agent such as poly(vinyl alcohol). The resulting emulsion is stirred until most of the organic solvent evaporated, leaving solid seeds or strands. Seeds and strands with different sizes (1-1000 μm diameter) and morphologies can be obtained by this method. This method is useful for relatively stable polymers like polyesters and polystyrene. However, labile polymers, such as polyanhydrides, may degrade during the fabrication process due to the presence of water. For these polymers, some of the following methods performed in completely anhydrous organic solvents are more useful.

Hot Melt Microencapsulation

Seeds can be formed from polymers such as polyesters and polyanhydrides using hot melt methods as described in Mathiowitz et al., *Reactive Polymers,* 6:275 (1987). In this method, the use of polymers with molecular weights between 3-75,000 Daltons preferred. In this method, the polymer first is melted and then mixed with the solid panicles of a substance to be incorporated that have been sieved to less than 50 μm. The mixture is suspended in a non-miscible solvent (like silicon oil), and, with continuous stirring, heated to 5° C. above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting seeds are washed by decantation with petroleum ether to give a free-flowing powder. Seeds and strands with diameters between 1 and 1000 μm are obtained with this method.

Solvent Extraction

This technique is primarily designed for polyanhydrides and is described, for example, in WO 93/21906, published Nov. 11, 1993. In this method, the substance to be incorporated is dispersed or dissolved in a solution of the selected polymer in a volatile organic solvent like methylene chloride. This mixture is suspended by stirring in an organic oil, such as silicon oil, to form an emulsion. Seeds that range between 1-300 μm can be obtained by this procedure.

Spray-Drying

Methods for forming seeds using spray drying techniques are well known in the art. In this method, the polymer is dissolved in an organic solvent such as methylene chloride. A known amount of a substance to be incorporated is suspended (insoluble agent) or co-dissolved (soluble agent) in the polymer solution. The solution or the dispersion then is spray-dried. Seeds ranging between 1 and 10 μm are obtained. This method is useful for preparing seeds tot imaging of the intestinal tract. Using the method, in addition to metal compounds, diagnostic imaging agents such as gases can be incorporated into the seeds.

Phase Inversion

Seeds can be formed from polymers using a phase inversion method wherein a polymer is dissolved in a good solvent, fine particles of a substance to be incorporated, such as a drag, are mixed or dissolved in the polymer solution, and the mixture is poured into a strong non solvent for the polymer, to spontaneously produce, under favorable conditions, polymeric seeds, wherein the polymer is either coated on the particles or the particles are dispersed in the polymer. The method can be used to produce microparticles in a wide range of sires, including, for example, about 100 nm to about 10 μm. Exemplary polymers which can be used include polyvinylphenol and polylactic acid. Substances which can be incorporated include, for example, imaging agents such as fluorescent dyes, or biologically active molecules such as proteins or nucleic acids.

Protein Microencapsulation

Protein seeds can be formed by phase separation in a non-solvent followed by solvent removal as described in U.S. Pat. No. 5,271,961 to Mathiowitz et al. Proteins which can be used include prolamines such as zein. Additionally, mixtures of proteins or a mixture of proteins and a bioerodable material polymeric material such as a polylactide can be used. In one embodiment, a prolamine solution and a substance to be incorporated are contacted with a second liquid of limited miscibility with the prolamine solvent, and the mixture is agitated to form a dispersion. The prolamine solvent then is removed to produce stable prolamine seeds without crosslinking or heat denaturation. Other prolamines which can be used include gliadin, hordein and kafirin.

Low Temperature Casting of Seeds

Methods for very low temperature casting of controlled release seeds are described in U.S. Pat. No. 5,019,400 to Gombotz et a in the method, a polymer is dissolved in a solvent together with a dissolved or dispersed substance to be incorporated, and the mixture is atomized into a vessel containing a liquid non-solvent at a temperature below the freezing point of the polymer-substance solution, which freezes the polymer droplets. As the droplets and non-solvent for the polymer are warmed, the solvent in the droplets thaws and is extracted into the non-solvent, resulting in the hardening of the seeds.

Strands can also be made using many of the above-techniques using extrusion technology to elongate the seeds into strands.

Hydrogel Seeds

Seeds made of gel-type polymers, such as alginate, are produced through traditional ionic gelation techniques. The polymer first is dissolved in an aqueous solution, mixed with a substance to be incorporated, and then extruded through a microdroplet forming device, which in some instances employs a flow of nitrogen gas to break off the droplet. A slowly stirred ionic hardening bath is positioned below the extruding device to catch the forming microdroplets. The seeds are left to incubate in the bath for twenty to thirty minutes in order to allow sufficient time for gelation to occur. Particle size is controlled by using various size extruders or varying either the nitrogen gas or polymer solution flow rates.

Chitosan seeds can be prepared by dissolving the polymer in acidic solution and crosslinking it with tripolyphosphate. Carboxymethyl cellulose (CMC) seeds can be pared by dissolving the polymer in acid solution and precipitating the microsphere with lead ions. Alginate/polyethylene imide (PEI) can be prepared in order to reduce the amount of car-

boxylic groups on the alginate microcapsule. The advantage of these systems is the ability to further modify their surface properties by the use of different chemistries. En the case of negatively charged polymers (e.g., alginate, CMC), positively charged ligands (e.g., polylysine, polyethyleneimine) of different molecular weights can be ionically attached.

Fluidized Bed

Particles, including seeds, can be formed and/or coated using fluidized bed techniques. One process is the Wurster air-suspension coating process for the coating of particles and seeds. The process consists of supporting the particles in a vertical column of heated air white the particles pass an atomizing nozzle that applies the coating material in the form of a spray. Enteric and film coating of seeds or strands by this process typically requites approximately 30 minutes. Suitable coating materials include, but are not limited to, cellulose acetate phthalate, ethylcellulose hydroxypropyl methylcellulose, polyethylene glycol, and zein.

The Wurster apparatus provides controlled cyclic movement of the suspended particles by a rising stream of warm air, the humidity, temperature, and velocity of the air regulated. An air-suspended or fluidized bed of particles has a random movement, if seeds or strands move in and out of a coating zone in a random manner, the coating can be applied only at a slow rate. The Wurster apparatus, however, provides better drying and eventually a more uniform coating by imparting a controlled cyclic movement without or with less randomness. A support grid at the bottom of the vertical column typically includes a course screen, e.g., 10 mesh, and a fine screen, e.g., 200 mesh. The fine screen offers considerably more resistance to the air flow than the coarse screen; thus, the greater amount of air flows through the coarse screen. The air flowing through coarse screen lifts the seeds or strands upward in the column. As the velocity of the air stream is reduced due to diffusion of the stream and resistance of the seeds or strands, the upward movement of the seeds or strands ceases. Then the seeds or strands enter the region of a still lower velocity air stream above the fine screen, where they dry and gently settle. As the dried and partially coated seeds or strands approach the grid, they are again introduced into the higher-velocity air stream and the coarse screen, and enter into another cycle.

Below the grid support for the coarse screen, the coating fluid is dispersed by atomization under pressure. A compressed-air inlet is connected to the atomizing the solution or slurry of the coating material. The seeds or strands, which are suspended above the coarse screen, have little, contact with each other, so the coating fluid is readily distributed onto the surface of the seeds or strands in the moving bed. As the cyclic movement of the seeds or strands continues, the seeds or strands are presented many times in many different positions to the atomized spray; therefore, a uniform coating is built up on the seeds or strands. Coating is controlled by the weight of the coated seeds or strands, formulation of the coating, temperature, time, and air velocity. Particle sizes can vary from about 50 μm to about 2 mm or greater.

IV. Method of Making Brachytherapy Strand For Implantation

One method of making a brachytherapy strand for implantation into a subject includes the steps of (a) providing a non-metal biocompatible component and a therapeutically active diagnostic or prophylactic component (herein referred to as "therapeutically active component"), optimally further including an imaging agent or tracer; (b) physically associating the biocompatible component and the therapeutically active component to from a combination product; and (c) forming the combination product into a strand having a size and shape suitable for passing through the bore of a needle having an interior diameter of less than about 2.7 millimeters (10 gauge), less than about 1.4 millimeters (15 gauge), or less than about 0.84 millimeters (18 gauge), or less than about 0.56 millimeters (24 gauge).

Referring to the drawings the are illustrated various different embodiments of the brachytherapy strands. Although there is no lower limit as to how small any dimension of strand can be, in many applications, those that are not able to pass through bores smaller than 0.3 mm are preferred. For example, in many applications where it is desirable for the implanted brachytherapy strands to maintain their orientation in the tissue, the strand should be large enough to stay lodged at the site of implantation in the desired orientation for a relatively long period, larger strands are preferred. In some cases, the selection of materials for use in the strand will affect its size. For instance, in versions of the strand where the biocompatible component is a stainless steel or titanium capsule, the walls of the capsule may need to be greater than a certain minimum size in order to maintain the structural integrity of the strand. In addition, in some applications, the strand should also be large enough to carry a sufficient amount of the therapeutically active component to be therapeutically active (i.e., a therapeutically effective amount or an amount that exerts a desired medically beneficial effect), in order to facilitate the passage of the strand through the bore of a needle while preventing jamming of the brachytherapy implantation needle bore (e.g., caused by clumping of several strands), it is also preferred that the diameter of strand be just slightly less than the diameter of the bore of the needle (e.g., 0.5-5% less).

For use with the needles used in many conventional brachytherapy strand implantation devices, brachytherapy seeds shaped into a cylinder (or rod) having a diameter of between about 0.8 to 3 millimeters and a length of up to 40 millimeters we preferred. Because many conventional brachytherapy strand applicators make use of brachytherapy implantation needles about 17 to 18 gauge in size, cylindrically shaped brachytherapy strands having a diameter of between about 0.8 and 1.1 mm and a length greater than the diameter (e.g., 2-10 mm) are preferred for use with such applicators. In particular, because many conventional brachytherapy strand applicators are designed to accept conventional radioactive brachytherapy strands that have a diameter of about 0.8 millimeters and a length of about 4.5 millimeters, brachytherapy strands of similar size are especially preferred.

Brachytherapy strands are not limited to those being cylindrical in shape, but rather can be any shape suitable for passing through the bore of a needle. For example, in any cases, the cross-sectional area of the strands can be cuboid, spheroid, ovoid, ellipsoid, irregularly shaped, etc. The ends of the strands can be rounded, squared, tapered, conical, convex, concave, scalloped, angular, or otherwise-shaped. The brachytherapy strands can be solid or have one or more cavities or pores (e.g., to increase the surface area of the strand exposed to the target tissue).

FIG. **1** is a schematic side view of a cylindrically shaped brachytherapy strand. FIG. **2** is a schematic side view of a hollow tube-shaped brachytherapy strand.

As one example, as illustrated in FIG. **2**, a brachytherapy strand **10** is shaped into a hollow tube **18** having a cylindrical cavity **20**. In preferred versions of strand **10**, cylindrical cavity **20** is sized to accept and envelop a standard-sized brachytherapy strand (e.g., one having a diameter of about 0.8 mm and a length of about 4.5 mm). For use, the strand **10** can be placed over the standard-sized brachytherapy strand, and introduced into the bore of a needle (sized to accept the enveloped strand) for implantation into a target tissue. The

strand **10** shown in FIG. **2** can also be used alone without being placed over a standard-sized brachytherapy strand, e.g., to increase the surface area exposed in the site of implantation. Hollow tube **18** can have any wall thickness or length suitable for wholly or partially enveloping a standard-sized brachytherapy strand and passing through the bore of a needle. Preferably it has a wall thickness between about 0.01 and 0.1 mm and a length of between about 1 to 4.5 mm.

Referring again to FIGS. **1** and **2**, biocompatible component **12** can be composed of any material suitable for implantation in a target tissue in an animal subject (e.g., a mammal such as a human patient) that can be associated with therapeutically active component such that all or part of the therapeutically active component will be delivered to the target tissue when the brachytherapy strand **10** is introduced into the implantation site, as discussed above. For ease of use, ease of manufacture, and for therapeutic advantages, it is preferred that the biocompatible component **12** be biodegradable (e.g., made of a substance other than titanium or stainless steel).

A skilled artisan can select the particular composition of the component **12** that is most suited for a given application. For example, where the strand **10** is intended to be used to slowly deliver the therapeutically active component **14** when implanted in a target tissue, a biocompatible and biodegradable material made up of a chemical composition of a polymer known to degrade at a desired rate when placed under conditions similar to those encountered in the implantation site can be selected for use as component **12**. Various characteristics of such biodegradable components are described, e.g., in *Biomaterials Engineering and Devices: Human Applications Fundamentals and Vascular and Carrier Applications*, Donald L. Wise et al (eds), Humana Press, 2000; *Biomaterials Science: An Introduction Materials in Medicine*, Buddy D. Ratner et al. (eds), Academic Press, 1997; and *Biomaterials and Bioengineering Handbook*, Donald L. Wise, Marcel Dekker, 2000. For example, by selecting an appropriate material for use as the biocompatible component **12** of the brachytherapy strand **10**, the duration of release of the therapeutically active component **14** from strand **10** can be varied from less than about an hour to more than about several months (e.g., 10 min., 30 min., 1 h., 2 h., 3 h., 6 h., 12 h., 1 day, 2 days, 3 days, 1 week, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 1 year, 2 years, or 3 years). Biocompatible component **12** is not limited to being biodegradable. For example, in some cases, component **12** can also be made of a non-biodegradable material such as stainless steel or titanium. In this case, biocompatible component **12** can be coated or otherwise associated with therapeutically active component **14**, such that component **14** will be delivered to a target tissue into which strand **10** is implanted. For instance, component **12** might take the form of a porous stainless steel or titanium cylinder having a plurality of pores through its outer surface, such pores being filled with or otherwise in communication with the component **14** such that the component **14** can diffuse from the strand **10** into the environment surrounding the strand **10** (e.g., a target tissue).

These can be tested for suitability in a given application by conventional clinical testing. For example, a test composition can be fashioned into a brachytherapy strand and implanted in a laboratory animal in a selected target tissue. The effects of the implanted compositions on the animal can then be monitored over a period of time. Those that prove to be biocompatible (e.g., not causing an undesired response such as calcification or an allergic response) and have a desired rate, of degradation and delivery of a therapeutically active component (if included in the test strand) can thus be identified.

As discussed above, the therapeutically active component **14** is a material that can be (a) implanted in a target tissue of an animal subject (e.g., a mammal such as a human patient) to exert an effect on the animal's physiology, and (b) associated with the biocompatible component **12** in the brachytherapy strand **10**. Myriad different substances can be used as the therapeutically active component **14**. See, e.g., Physician's Desk Reference, The Merck Index, and USP DI® 2000 published by U.S. Pharmacopeia. For example, the therapeutically active component **14** can include a small molecule drug (e.g., a non-peptide or non-nucleic acid-based molecule with a molecular weight generally less than 5 kDa) such as a chemical with known anti-cancer properties, it can also include a biologic such as a polypeptide (e.g., an antibody or a cytokine) or nucleic acid (e.g., an expression vector). For example, where the strand **10** is intended to be used as a primary treatment for prostate cancer, the therapeutically active substance **14** can include an anti-neoplastic drug such as paclitaxel (taxol), cisplatin, or 5-fluorouracil; or a hormone such as leuprolide. As another example, whole the strand **10** is intended to be used as an adjuvant to radiation treatment for prostate cancer, the therapeutically active substance **14** can include a radio-sensitizing agent such as tirapazamine, BUdR, IUdR, or etanidazole. Because brachytherapy strand **10** allows in situ drug delivery to a tissue, the therapeutically active substance **14** may include a drug that is usually considered too toxic to treat a given condition if given systemically, e.g., tirapazamine or camptothecin.

As indicated in the above description of the brachytherapy strand **10** shown in FIGS. **1** and **2**, the biocompatible component **12** is associated with the therapeutically active component **14**. As used herein, when referring to the biocompatible component **12** and the therapeutically active component **14**, the phrase "associated with" means physically contacting. Thus, in the strand **10**, the association of the biocompatible component **12** with the therapeutically active component **14** can take many forms. For example, the biocompatible component **12** and the therapeutically active component **14** can be combined into a mixture as shown in FIGS. **1** and **2**. This mixture can have a uniform or non-uniform distribution of components **12** and **14**. The brachytherapy strand **10** shown in FIG. **1** is an example of a uniform mixture of components **12** and **14**. The brachytherapy strand **10** of this example can be made by simply mixing together the biocompatible component **12** and the therapeutically active component **14** to form a combination product and then forming the product into the desired size and shape, e.g., using a mold.

Although the brachytherapy strands shown in FIGS. **1** and **2** include mixtures of discrete particles dispersed through a matrix consisting of the therapeutically active component **14**, in other versions of brachytherapy strand **10**, components **12** and **14** are combined in a single particle or in a larger mass without discrete particles (e.g., a pellet the size and shape of brachytherapy strand **10**). For example, biocompatible component **12** and therapeutically active component **14** can be dissolved into a liquid and then dried or cured to form strands or a larger pellet made up of a homogeneous distribution of components **12** and **14**. (see, e.g., Ramirez et al., *J. Microencapsulation* 16:105, 1999).

The skilled artisan can select the size according to the desired properties and particular properties of the microsphere constituents. In one variation of this, the strands are also made to include magnetic elements. The strands can then be molded or compressed together into the desired shape and size of brachytherapy strand **10**. The larger pellet can likewise be sculpted, extruded, molded or compressed into the desired shape and size of brachytherapy strand **10**. Alternatively, the

liquid mixture of components **12** and **14** can be poured into a mold defining the shape and size of brachytherapy strand **10**, and then cured in the mold. Brachytherapy strands having components **12** and **14** combined in a single particle or in a larger mass (rather than discrete particles of each are advantageous for delivering the therapeutically active component **14** into a target tissue over longer time periods.

In other embodiments of strand **10**, components **12** and **14** are not necessarily homogeneously mixed in the strand **10**. Rather they can be positioned in different areas of the strand **10**. For example, components **12** and **14** can be separately fashioned into discrete sections, strips, coils, tubes, etc. The discrete sections, strips, coils, tubes, etc. of the component **12** can then be combined (e.g., by molding together, adhering, structurally interlocking, etc.) with the discrete sections, strips, coils, tubes, etc. of the component **14** to form the strand **10**. In another embodiment, the strand **10** shown in FIG. **2** can be modified by filling the cylindrical cavity **20** with a hydrogel, including a therapeutically active substance, and capping off the ends of the hollow tube **18**.

These variations are more clearly understood by reference to the following figures. FIGS. **3**A-**3**I are strands with inert spacers **20**, interspersed for cutting (FIG. **3**A); with pop-up wings **22** to prevent migration or shifting after implanting (FIG. **3**B); with a radiopaque strip **30** running through it (FIG. **3**C); with cross-style stabilizers **32** (FIG. **3**D); with male **34** and female **36** ends to facilitate joining, e.g., in a ring (FIG. **3**E); with indentations **38** for cutting or breaking into smaller strands (FIG. **3**F); with a stabilizer, such as bumps **40** (FIG. **3**G); as braided strand **42** (FIG. **3**H); and strands knotted together **44** (FIG. **3**I). FIGS. **4**A and **4**B are a strand **50** with radioactive seeds **52** interspersed (perspective view, FIG. **4**A; cross-sectional view, FIG. **4**B).

The foregoing combination products (i.e., at least one biocompatible component mixed with at least one therapeutically active component) can be used in the brachytherapy strands by forming them into a size and shape suitable for passing through the bore of a needle such as one in a conventional brachytherapy strand implantation device. Referring now to FIGS. **3**A-I, in others, a brachytherapy strand **10** includes a biocompatible component **12** associated with a therapeutically active component **14**, and a radiopaque marker **30** (not shown except in FIG. **3**C) attached to the biocompatible component **12** and/or the therapeutically active component **14**. Radiopaque marker **30** allows for the position of brachytherapy strand **10** to be determined using standard X-ray imaging techniques (e.g., fluoroscopy) after strand **10** has been implanted in a target tissue. Proper positioning of strand **10** and spacing of a plurality of brachytherapy strands in a given target tissue is important for ensuring that the therapeutically active component **14** is delivered adequately to the site of the disease in the target tissue.

As indicated above, radiopaque marker **30** is attached to strand **10** via the biocompatible component **12** and/or the therapeutically active component **14**. The exact manner in which radiopaque marker **30** is attached to strand **10** can is not critical so long as (a) the strand **10** can be passed through the bore of a brachytherapy implantation needle and (b) the attachment allows the position of strand **10** to be readily detected by X-ray imaging. A description of some different examples of how marker **30** can be associated with strand is presented in FIGS. **3**A-F. In the embodiment shown in FIG. **3**A, the radiopaque marker **30** in the form of a ribbon, filament, strip, thread, or wire is placed in the center and along the length of cylindrical strand **10**. In FIG. **3**B, the radiopaque marker **30** takes the form of two end caps placed at both ends of cylindrical strand **10**. In the embodiment illustrated in FIG. **3**C, the radiopaque marker **30** is a coil made of a radiopaque substance running through the length of cylindrical strand **10** as shown. In FIG. **3**D, the radiopaque marker **30** takes the form of two beads or pellets placed at two locations along cylindrical strand **10**. In the embodiment shown in FIG. **3**E, the radiopaque marker **30** takes the form of two bands or rings placed at two locations along the (Inter surface of cylindrical strand **10**. In the strand **10** shown in FIG. **3**F, the radiopaque marker **30** takes the form of a mesh formed into cylindrical shape. In the strand **10** shown in FIG. **3**G, the radiopaque marker **30** is dispersed throughout the strand in a stippled pattern.

FIGS. **4**A and **4**B are a strand with radioactive seeds interspersed (perspective view, FIG. **4**A cross-sectional view, FIG. **4**B).

A particularly preferred embodiment of a brachytherapy strand having a radiopaque marker is one in which the radiopaque marker is a polymer. In one version of this embodiment, radiopaque polymers are combined with a biocompatible component and a therapeutically active component to form a brachytherapy strand that can be visualized by X-ray imaging. Alternatively, the radiopaque polymer can serve as the biocompatible component. For example, strands made of a radiopaque polymer are co-mingled with strands containing a biocompatible component and strands containing (e.g., encapsulating) a therapeutically active component for strands containing both a biocompatible component and a therapeutically active component). The co-mingled strands are then molded into a radiopaque brachytherapy strand. As another example, the radiopaque polymer, the bib compatible component, and the therapeutically active component can be mixed together into a liquid, and the liquid can be cured to form a solid pellet that can be sculpted, molded, compressed, or otherwise made into the size and shape of a brachytherapy strand. An advantage of preparing a radiopaque brachytherapy strand in this manner is that, after implantation, the entire strand can be visualized by X-ray imaging rather than only a portion of a strand (e.g., as occurs with strands utilizing conventional markers).

FIGS. **5**A-**5**D are perspective views of strands after introduction into breast adjacent to lumpectomy site (larger circle) below the nipple (smaller circle) (FIG. **5**A); strands conforming to shape of breast with patient now upright, lumpectomy site is shown as, larger black circle, nipple as smaller circle (FIG. **5**B); strand deployed as a coil (FIG. **5**C); and strands deployed as rings around lumpectomy site (FIG. **5**D).

FIG. **6** is a magnified depiction of microfabricated polyimide hairs. By covering the brachytherapy seed or strand with these polyimide hairs, the problem of seed migration can be effectively overcome. Seed migration involves movement of seeds from their implanted location, usually during the interval immediately following wed placement. Two precipitating causes are felt to be a recoil effect in tissue as it springs back from deformation caused by the seed introducer needle, and suction along the exit path caused by the needle as it is withdrawn after depositing seeds. Several papers in the literature have addressed this issue (see for example. Tapen et al., *IJROBP* 1998; 42:1063-7, Merrick et al., *IJROBP* 2000; 46:215-20, Poggi et al., IJROBP 2003; 56:1248-51).

One method of overcoming this problem is to secure seeds together in a coaxial array within suture strand material such that seeds are kept at a fixed distance from one another. Another approach is to attach each seed to an interlocking peg (see Grimm U.S. Pat. No. 6,450,939B1), again to create a fixed arrangement. However, these systems are fixed by definition, and can present logistical problems when one is working with irregularly shaped targets, or targets that are split by

intervening tissue that one wishes to avoid. Furthermore, the strands themselves can migrate, skewing the dosimetry for an entire row of seeds.

Prior art brachytherapy seeds have not satisfactorily addressed the issue of limiting individual seed movement along the needle track. Giem et al have succeeded in producing microfabricated polyimide bans, and showed that their artificial hairs produce capillary and van der Waals forces which impart particular adhesive properties (Giem et al., *Nature Materials* 2003; 2:461-3). These polyimide hairs have been constructed based on the structure of gecko foot-hairs (setae) which have been shown to have astounding adhesive properties. The polyimide hairs have diameters from 0.24 micrometers, heights from 0.15-2 micrometers, and periodicity from 0.445 micrometers.

The hairs were made as long as possible, and have sufficient flexibility so that individual tips can attach to uneven surfaces all at the same time, and do not break, curl or tangle. Care was taken not to make the hairs too thin, lest they fall down, or too dense, lest they bunch. In order to overcome the problems associated with seed and strand migration, setae technology is used to cover or coat the biodegradable seeds and strands with hairs that impart comparable adhesive potential.

When seeds and strands are implanted into tissues, those tissues are unevenly distributed around the implanted material. The compliant setal structure permits conformance to the shape of a contacting structure, increasing the magnitude of the attractive van der Waals forces as the tiny hairs act together. Similarly, as the seeds and strands are pushed out of their introducing needle, they are dragged over the tissue, which increases setal adhesion. Larger setae create larger sticking forces from larger setal contact areas.

Finally, the tissue is moist since it is living tissue, and setae have improved adhesive properties when they are moist. All of these factors make biodegradable setae (protrusions) an ideal solution to seed/strand migration [see FIG. **6**].

FIGS. **7**A and **7**B illustrate brachytherapy strand geometries such that the brachytherapy strand has one or more conduits running along the length of the strand. These conduits can be pre-filled or fillable, and are useful in the delivery of therapeutic and diagnostic agents to the surrounding implanted tissue. The agents need not be biodegradable themselves, but should be fluid enough to pass through the conduits. Optionally, there can be a pore, series of pores, or network of pores and conduits along the strands through which the agents flow out into the surrounding tissue. In another embodiment, there can be a portal that can be accessed with a needle or other introducer instrument through the skin, or the portal can protrude out of the body via a percutaneous connection to the conduit system. The radioactive material in the strand, if present, can be separated from the conduit system by intervening nonradioactive material. Sundback et al described a similar system in *Biomaterials* 2003; 24:1119-30 wherein the conduits were used to contour nerve growth.

The therapeutically active agent **14** in strand **10** including the sealed container **40** can be any of those agents described above. Preferably, however, agent **14** is selected to provide an enhanced effect when used in combination with the radioisotope to treat a particular diseased tissue, as discussed above.

The radioisotope can be any substance that emits electromagnetic radiation (e.g., gamma-rays or X-rays), beta-particles or alpha particles and is suitable for use in brachytherapy strand **10**. Examples of such substances include those that decay principally by electron capture followed by X-ray emission such as palladium-103 and iodine-125; isotopes that decay by the emission of beta-particles such as gold-198, gold-199, yttrium-90, and phosphorus-32; isotopes that decay with the emission of both beta-particles and gamma-rays such as indium-192; and isotopes that decay with the emission of alpha-particles such as americium-241. Also useful is gadolinium-157, e.g., for use in boron neutron capture therapy, and californium-252, rhenium-188, samarium 153, indium-111, ytterbium-169, and holmium-166. For the treatment of prostate cancer, palladium-103 and iodine-125 are preferred as these have been the subject of much clinical investigation for the treatment of the disease. The amount of radioactivity of radioisotope can vary widely. For example, when using palladium-103 or iodine-125, an exemplary amount to treat prostate cancer is respectively about 1.5 mCi and 033 mCi per strand, if about 50-150 strands are used at the time of implantation. In other applications the radioactivity per strand can range from about 0.01 mCi to about 100 mCi.

In one embodiment, the radioisotope can be mixed with and then configured into strands, or it can be encapsulated by the biocompatible component to form strands. The radioactive strands cart be molded or otherwise sized and shaped into a brachytherapy strand suitable for implantation via a brachytherapy implantation device, in one version of this embodiment, the biocompatible component is biodegradable such that the radioisotope contained by this component is gradually released from the strand. Alternatively, the biocompatible component and radioisotope can be mixed together and configured as an amorphous pellet having the size and shape of a brachytherapy strand suitable for implantation via a brachytherapy implantation device.

In a preferred embodiment in which the brachytherapy strand contains radionuclide, the strand is coated with a non radioactive biodegradable coating which degrades at a rate slower than that which allows the radioactivity to leach out, so that radioactivity is not released—i.e., the radioactivity has already fully decayed.

FIGS. **8**A, **8**B and **9** depict the addition of polymeric anchoring structures to brachytherapy strands. Biodegradable seeds may also be equipped with as similar system, but on a smaller scale. As noted above, migration can be problematic. Built-in ridges, humps, and related structures can ameliorate this problem to some extent, but will not completely eliminate it.

Biodegradable shape memory polymeric (Lendlein et al., *Science* 2002; 296:1673-6) structures which deploy to their pre-trained shape after implantation in order to maintain the seeds in the desired location may also be used. Such structures can ideally include grapple-shaped anchors at the ends of a brachytherapy strand [see FIG. **8**A]. These hooks deploy following introduction of the strand into the target tissue. Similar structures can be interspersed the length of the strand, oriented such that the strand becomes locked in position [see FIG. **8**B]. The same concept can be used to brace or center the strands within a target tissue in instances where that tissue contains a cavity, defect or other irregular space that might otherwise kink, bend, or offset the strand [see FIG. **9**].

These may be bristle-like, ring-shaped, or alternative shapes depending upon the choice made by those skilled in the art. Similarly, they can space apart adjacent strands, thereby avoiding clumping or hunching. Optionally, these structures may or may not contain the therapeutic or diagnostic agents. The shape memory structures are activated by heat from the implanted tissue, or are preheated prior to implantation to trigger their deployment.

As with the shape memory polymer above, electroactive polymers (EAPs) or polymer hybrids may be used for stabilization, spacing, or related purposes. Hybrid substrates can

include biodegradable polymer/semiconductor composites. These components expand, contract, bend, or otherwise change shape or size displacement upon exposure to an applied voltage. These types of changes can be induced with very low voltage input which can be achieved without harming the host tissue. Pelrine described this style device in U.S. Pat. No. 6,545,384 B1, as did Kornbluh in U.S. Pat. No. 6,586,859B2.

Electronic EAPs can include ferroelectric polymers, dielectric polymers, electrorestrictive graft elastomers, electro-viscoelastic elastomers, liquid crystal elastomer materials, or other related polymers or organic substances, ionic EAPs can include ionic polymer gels, ionomeric polymer-metal composites, conductive polymers, carbon nanotubes, or other related polymers or organic substances (see for example Bar-Cohen et al., ed., *Electroactive Polymers and Rapid Prototyping: Materials Research Society Symposium Proceedings*, Materials Research, 2002; *Applications of Electroactive Polymers*, (Stienen, ed.), Kluwer Academic Publishers, 1993; Zhang et al., *Nature* 2002; 419:284-7): Scheibe et al. described the use of biomolecular templates as conducting nanowires in PNAS 2003; 100:4527-32. In this instance, amyloid formed by prions was the biomolecular substance used to create the nanowires. Various physico-chemical factors, such as light, temperature, and pH can be applied to the "small polymers" or other substrates to achieve similar configuration modification.

Spacers can be made of a biocompatible material that can be used to join two brachytherapy seeds. See, e.g., U.S. Pat. No. 6,010,446. The biocompatible material can be either biodegradable or non-biodegradable. For example, spacers can be made of catgut or a like materials Spacers designed for use with conventional radioactive brachytherapy seeds can be used in chain. For example, Ethicon, Inc. (Cincinnati, Ohio) manufactures the PG 940 non-sterile autoclavable spacer for indigo (Cincinnati, Ohio) that is sold in conjunction with an Express Seed Cartridge. In addition, Medical Device Technologies, Inc. (Gainesville, Fla.) distributes a p-sterilized 5.5 mm long absorbable pre-cut spacer that is made of collagen (Look®, model number 1514b). Materials for use as the spacer are also manufactured by Surgical Specialties Corp. (Reading Pa.). Where the spacer is made of a relatively flexible material, the chain can be relatively flaccid.

Where the brachytherapy strand or linker is formed of an elastic polymer such as elastin-like peptides, polyhydroxyalkanoates (PHAs) or poly(glycol-sebacate), or some protein, the strand or chain is becomes high deformable. Such deformability is particularly advantageous when implanting tissues or organs whose shape may become distorted by normal body motion, such as the breasts or viscera. Where the chain is endowed with the flexibility of an elastic polymer or similar substance, the chain may be considered to be variably flexible rather than rigid or flaccid. The precise degree of flexibility will depend upon the composition of the carrier matrix. Those skilled in the art will be accustomed to selecting the ration of component substances in the carrier matrix such that the desired degree or flexibility is achieved. This flexibility, rather than being simply linear or curved, can be in any direction. In some embodiments, the chain may be spiral-shaped or otherwise twisted, springy, or bent to conform to the desired shape. In other embodiments, the chain can form a lattice or mesh whereby one or more chains can be interconnected through baking mechanisms, knots ties, welds, fusions, or other methods known to those skilled in the art. In yet another embodiment, the chain may be introduced into the target tissue in one shape, only to be purposefully or intentionally modified or altered to another advantageous shape thereafter.

Spacers can be connected to seed by any means known. For example, spacer can be connected to seed by direct attachment such as by gluing, crimping, or melting. Spacers can be attached to any portion of the seed. For rod or cylinder-shaped seeds, to facilitate implantation, it is generally preferred that spacers are attached to the ends of the seeds so that the ends are adjacent to one another when the chain is inserted into the barrel of a brachytherapy implantation needle, in one preferred embodiment, the spacer and seed are indistinguishably linked such that no seams, welds, or joints are visible. In another embodiment, the spacer may be of a different color, texture, diameter, hardness, or shape for easy identification and demarcation. This can include a translucent coloration. In still another embodiment, the spacer may be indented or otherwise marked somewhere along its length as an indication of where the seed/spacer chain can be safely cut, spliced, broken, or otherwise separated without exposing active therapeutic substances such as radionuclides that are contained within the seed.

In another embodiment, spacers may be emitted in favor of a continuous array of seeds that may form a chain or strand. This is especially advantageous when implanting an organ such as the breast, where discrete seeds are not necessarily required to achieve the desired dispersement of radioactivity and/or other therapeutic substances. The continuous seed array without interruption by spacer is especially preferred when the implanted strands contain an elastic polymer or other flexible carrier for use in a mobile organ or tissue. In yet another embodiment, spacers may be located at varying distances from one another, separated by different lengths of continuous seed arrays, depending upon the clinical circumstances. Depending upon the discretion of the clinician, more than one continuous seed and/or spacer array may be implanted along a given row to achieve the desired effect in tissue.

Where spacers are used, spacer and seed, however, need not be physically attached to each other. Rather they can also be associated with each other by placing each with within the lumen of a tube. The tube can be used to load a brachytherapy seed implantation device with a plurality of spacers and seeds in any sequence. For example, the brachytherapy seed implantation device can loaded with one (or 2, 3, 4, 5, or more) spacer being interposed between every two seeds. Similarly, the brachytherapy seed implantation device can be loaded with one (or 2, 3, 4, 5, or more) seed being interposed between every two spacers.

VI. Methods of Implantation

The brachytherapy strands are implanted into a target tissue within a subject (e.g., a human patient or a non-human animal) by adapting known methods for implanting conventional radioactive brachytherapy seeds into a tissue. For example, the brachytherapy strands can be implanted using one or more implantation needles; Henschke, Scott, or Mick applicators; or a Royal Marsden gold grain gun (H, J. Hodt et al., *British J. Radiology, pp.* 40-421, 1952). A number of suitable, implantation devices are described in, e.g., U.S. Pat. Nos. 2,269,963; 4,402,308; 5,860,909; and 6,007,474.

In many applications to treat a given target tissue with a therapeutic agent, it is desirable (or even ideal) to fully saturate the target tissue with the therapeutic agent, while avoiding under- or over-dosing the target tissue. This can be achieved by implanting the brachytherapy strands into a target tissue using a brachytherapy implantation device so that a precise number of strands can be implanted in precise loca-

tions within the target tissue. By previously calculating the rate of diffusion of the therapeutically active substance under experimental conditions (e.g., using tissue from animal models), an appropriate dosage can be delivered to the target tissue. Because use of brachytherapy implantation devices allows the brachytherapy strands to be implanted in any number of different desired locations and/or patterns in a tissue, this method is advantageous over methods where a drug or drug impregnated matrix is simply placed on the surface of a tissue or manually inserted into a surgically dissected tissue.

In one preferred method of use, the strands are introduced into the target organ through a puncture site with a brachytherapy needle, obviating the need for an incision, suturing of a catheter, tracheostomy, or prolonged insertion of an often uncomfortable or painful metallic or plastic foreign body into the patient. In the case of the base of tongue, the hairpin needles are withdrawn following loading of the strands, thereby limiting the degree of swelling that occurs and possibly sparing the patient the need for a tracheostomy. In the case of a lumpectomy for removal of a breast cancer, the strands can be placed in the same fashion as temporary iridium-192 or iodine-125 metallic seed strands, but without the sutures and buttons anchoring the catheters or needles and strands to the skin for retrieval later.

I claim:

1. A seed, for implantation into a subject, comprising: a marker component configured to allow for the determination of the position of the seed within a target tissue, the marker component having a length extending along a centerline of the marker component between a first end and a second end and having a substantially continuous wall bounding a hollow interior; and a therapeutic, prophylactic, and/or diagnostic agent, wherein the agent is disposed within the hollow interior; wherein the length of the marker component is greater than the diameter of the hollow interior and wherein the substantially continuous wall includes at least one opening adapted to allow the agent to pass out of the hollow interior.

2. The seed according to claim **1** wherein the marker component has a maximum length of 10 mm.

3. The seed according to claim **1** wherein at least one of the marker component and the agent is imageable.

4. The seed according to claim **3** wherein the marker component is imageable.

5. The seed according to claim **1** wherein the marker component comprises one or more structures that resist migration of the seed from the site of implantation, one or more biodegradable structures effective to maintain orientation in tissue, one or more compliant setal or hair structures which impart adhesive properties upon implantation into a target tissue, or combinations thereof.

6. The seed according to claim **5** wherein the marker component comprises one or more structures that resist migration of the seed from the site of implantation, one or more biodegradable structures effective to maintain orientation in tissue or combinations thereof.

7. The seed of claim **6**, wherein the structures to maintain location or orientation comprise a smart polymer, a shape memory polymer, or other substrate to achieve configuration modification.

8. The seed according to claim **6** wherein the structure includes an anchor.

9. The seed according to claim **1** wherein the marker component comprises a biocompatible component and the agent is dispersed in a coating on the biocompatible component.

10. The seed according to claim **1** wherein the agent is mixed together with the marker component.

11. The seed according to claim **10** wherein the marker component is biodegradable.

12. The seed according to claim **11** wherein the marker component is configured to degrade over time at the implantation site and release the agent by controlling the rate of degradation and/or release rate at the implantation site.

13. The seed according to claim **1** wherein the marker component comprises a coil.

14. The seed according to claim **1** wherein the at least one opening comprises a plurality of pores.

15. The seed according to claim **1** wherein the target tissue includes a cancer or a lumpectomy site.

16. The seed according to claim **1** wherein the agent is selected from the group consisting of an anti-inflammatory, anti-coagulant, cytostatic, antibiotic, anti-neoplastic, vasodilator, anti-viral, immunosuppressive, growth factor, pro-agent, hormone, radiotherapeutic, radiopaque, peptide, protein, enzyme, or combinations thereof.

17. A seed comprising a marker component and a therapeutic, prophylactic, and/or diagnostic agent, the agent, marker, or both, being imageable, the marker component having a length extending along a centerline of the marker component between a first end and a second end and having a substantially continuous wall along the length, the substantially continuous wall bounding a hollow interior and at least partially enveloping the agent within the hollow interior, and wherein the length of the marker component is greater than an average diameter of the hollow interior and the substantially continuous wall includes at least one opening adapted to allow the agent to pass out of the hollow interior.

18. The seed according to claim **17**, wherein the marker component comprises an imageable substrate and the agent is dispersed in a coating on the substrate.

19. The seed according to claim **17**, wherein the marker component comprises a substrate comprising a biodegradable material further comprising the agent.

20. A seed comprising: a marker component configured to mark the position of the seed in a target tissue, the marker component comprising a tube having open ends, and having a substantially continuous wall bounding a hollow interior; and a therapeutic, prophylactic, and/or diagnostic agent, wherein the agent is disposed within the hollow interior of the tube, and wherein the open ends facilitate passing of the agent out of the hollow interior of the tube to the environment surrounding the seed; and wherein the seed further comprises a plurality of openings that extend through the wall, and wherein the plurality of openings facilitate the passing of the agent out of the hollow interior of the tube into the surrounding tissue.

* * * * *

EXHIBIT F

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NEXPLANON safely and effectively. See full prescribing information for NEXPLANON.

NEXPLANON® (etonogestrel implant)
Radiopaque
Subdermal Use Only
Initial U.S. Approval: 2001

----------INDICATIONS AND USAGE----------
NEXPLANON is a progestin indicated for use by women to prevent pregnancy. (1)

---------- DOSAGE AND ADMINISTRATION ----------
Insert one NEXPLANON subdermally just under the skin at the inner side of the non-dominant upper arm. NEXPLANON must be removed no later than by the end of the third year. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------
NEXPLANON consists of a single, radiopaque, rod-shaped implant, containing 68 mg etonogestrel, pre-loaded in the needle of a disposable applicator. (3)

----------CONTRAINDICATIONS----------
- Known or suspected pregnancy. (4)
- Current or past history of thrombosis or thromboembolic disorders. (4, 5.4)
- Liver tumors, benign or malignant, or active liver disease. (4, 5.7)
- Undiagnosed abnormal genital bleeding. (4, 5.2)
- Known or suspected breast cancer, personal history of breast cancer, or other progestin-sensitive cancer, now or in the past. (4, 5.6)
- Allergic reaction to any of the components of NEXPLANON. (4, 6)

---------- WARNINGS AND PRECAUTIONS----------
- Insertion and removal complications: Pain, paresthesias, bleeding, hematoma, scarring or infection may occur. (5.1)
- Menstrual bleeding pattern: Counsel women regarding changes in bleeding frequency, intensity, or duration. (5.2)
- Ectopic pregnancies: Be alert to the possibility of an ectopic pregnancy in women using NEXPLANON who become pregnant or complain of lower abdominal pain. (5.3)
- Thrombotic and other vascular events: The NEXPLANON implant should be removed in the event of a thrombosis. (5.4)
- Liver disease: Remove the NEXPLANON implant if jaundice occurs. (5.7)
- Elevated blood pressure: The NEXPLANON implant should be removed if blood pressure rises significantly and becomes uncontrolled. (5.9)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women using NEXPLANON. (5.11)

---------- ADVERSE REACTIONS ----------
Most common (≥10%) adverse reactions reported in clinical trials were change in menstrual bleeding pattern, headache, vaginitis, weight increase, acne, breast pain, abdominal pain, and pharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Drugs or herbal products that induce certain enzymes, such as CYP3A4, may decrease the effectiveness of progestin hormonal contraceptives or increase breakthrough bleeding. (7.1)

---------- USE IN SPECIFIC POPULATIONS ----------
- Pregnant women: NEXPLANON should be removed if maintaining a pregnancy. (8.1)
- Overweight women: NEXPLANON may become less effective in overweight women over time, especially in the presence of other factors that decrease etonogestrel concentrations, such as concomitant use of hepatic enzyme inducers. (8.8)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NEXPLANON® is indicated for use by women to prevent pregnancy.

2 DOSAGE AND ADMINISTRATION

The efficacy of NEXPLANON does not depend on daily, weekly or monthly administration.

All healthcare providers should receive instruction and training prior to performing insertion and/or removal of NEXPLANON.

A single NEXPLANON implant is inserted subdermally in the upper arm. To reduce the risk of neural or vascular injury, the implant should be inserted at the inner side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus. The implant should be inserted subdermally just under the skin, avoiding the sulcus (groove) between the biceps and triceps muscles and the large blood vessels and nerves that lie there in the neurovascular bundle deeper in the subcutaneous tissues. An implant inserted more deeply than subdermally (deep insertion) may not be palpable and the localization and/or removal can be difficult or impossible *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)].* NEXPLANON must be inserted by the expiration date stated on the packaging. NEXPLANON is a long-acting (up to 3 years), reversible, hormonal contraceptive method. The implant must be removed by the end of the third year and may be replaced by a new implant at the time of removal, if continued contraceptive protection is desired.

2.1 Initiating Contraception with NEXPLANON

IMPORTANT: Rule out pregnancy before inserting the implant.

Timing of insertion depends on the woman's recent contraceptive history, as follows:

- No preceding hormonal contraceptive use in the past month

  NEXPLANON should be inserted between Day 1 (first day of menstrual bleeding) and Day 5 of the menstrual cycle, even if the woman is still bleeding.

  If inserted as recommended, back-up contraception is not necessary. If deviating from the recommended timing of insertion, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.

- Switching contraceptive method to NEXPLANON

  Combination hormonal contraceptives:

  NEXPLANON should preferably be inserted on the day after the last active tablet of the previous combined oral contraceptive or on the day of removal of the vaginal ring or transdermal patch. At the latest, NEXPLANON should be inserted on the day following the usual tablet-free, ring-free, patch-free or placebo tablet interval of the previous combined hormonal contraceptive.

  If inserted as recommended, back-up contraception is not necessary. If deviating from the recommended timing of insertion, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.

  Progestin-only contraceptives:

  There are several types of progestin-only methods. NEXPLANON should be inserted as follows:

  - Injectable Contraceptives: Insert NEXPLANON on the day the next injection is due.
  - Minipill: A woman may switch to NEXPLANON on any day of the month. NEXPLANON should be inserted within 24 hours after taking the last tablet.

- Contraceptive implant or intrauterine system (IUS): Insert NEXPLANON on the same day the previous contraceptive implant or IUS is removed.

If inserted as recommended, back-up contraception is not necessary. If deviating from the recommended timing of insertion, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.

- Following abortion or miscarriage
  - First Trimester: NEXPLANON should be inserted within 5 days following a first trimester abortion or miscarriage.
  - Second Trimester: Insert NEXPLANON between 21 to 28 days following second trimester abortion or miscarriage.

If inserted as recommended, back-up contraception is not necessary. If deviating from the recommended timing of insertion, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.

- Postpartum
  - Not Breastfeeding: NEXPLANON should be inserted between 21 to 28 days postpartum. If inserted as recommended, back-up contraception is not necessary. If deviating from the recommended timing of insertion, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.
  - Breastfeeding: NEXPLANON should be inserted after the fourth postpartum week *[see Use in Specific Populations (8.3)]*. The woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.

2.2 Insertion of NEXPLANON

The basis for successful use and subsequent removal of NEXPLANON is a correct and carefully performed subdermal insertion of the single, rod-shaped implant in accordance with the instructions**.** Both the healthcare provider and the woman should be able to feel the implant under the skin after placement.

All healthcare providers performing insertions and/or removals of NEXPLANON should receive instructions and training prior to inserting or removing the implant. Information concerning the insertion and removal of NEXPLANON will be sent upon request free of charge [1-877-467-5266].

Preparation

Prior to inserting NEXPLANON carefully read the instructions for insertion as well as the full prescribing information.

Before insertion of NEXPLANON, the healthcare provider should confirm that:

- The woman is not pregnant nor has any other contraindication for the use of NEXPLANON *[see Contraindications (4)]*.
- The woman has had a medical history and physical examination, including a gynecologic examination, performed.
- The woman understands the benefits and risks of NEXPLANON.
- The woman has received a copy of the Patient Labeling included in packaging.
- The woman has reviewed and completed a consent form to be maintained with the woman's chart.
- The woman does not have allergies to the antiseptic and anesthetic to be used during insertion.

Insert NEXPLANON under aseptic conditions.

The following equipment is needed for the implant insertion:

- An examination table for the woman to lie on
- Sterile surgical drapes, sterile gloves, antiseptic solution, sterile marker (optional)
- Local anesthetic, needles, and syringe
- Sterile gauze, adhesive bandage, pressure bandage

Insertion Procedure

Step 1. Have the woman lie on her back on the examination table with her non-dominant arm flexed at the elbow and externally rotated so that her wrist is parallel to her ear or her hand is positioned next to her head (Figure 1).

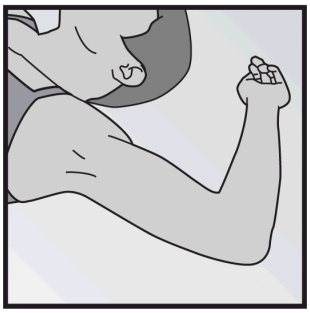


Figure 1

Step 2. Identify the insertion site, which is at the inner side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus, avoiding the sulcus (groove) between the biceps and triceps muscles and the large blood vessels and nerves that lie there in the neurovascular bundle deeper in the subcutaneous tissue (Figure 2). **The implant should be inserted subdermally just under the skin** *[see Warnings and Precautions (5.1)]*.

Step 3. Make two marks with a sterile marker: first, mark the spot where the etonogestrel implant will be inserted, and second, mark a spot a few centimeters proximal to the first mark (Figure 2). This second mark will later serve as a direction guide during insertion.

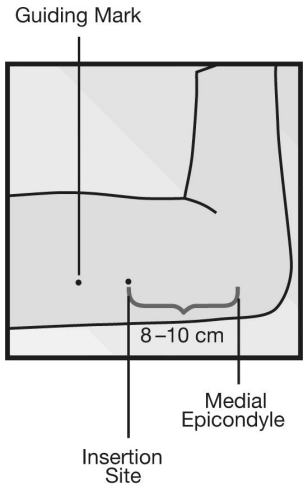


Figure 2

Step 4. Clean the insertion site with an antiseptic solution.

Step 5. Anesthetize the insertion area (for example, with anesthetic spray or by injecting 2 mL of 1% lidocaine just under the skin along the planned insertion tunnel).

Step 6. Remove the sterile preloaded disposable NEXPLANON applicator carrying the implant from its blister. The applicator should not be used if sterility is in question.

Step 7. Hold the applicator just above the needle at the textured surface area. Remove the transparent protection cap by sliding it horizontally in the direction of the arrow away from the needle (Figure 3). If the cap does not come off easily, the applicator should not be used. You can see the white colored implant by looking into the tip of the needle. **Do not touch the purple slider until you have fully inserted the needle subdermally, as it will retract the needle and prematurely release the implant from the applicator.**

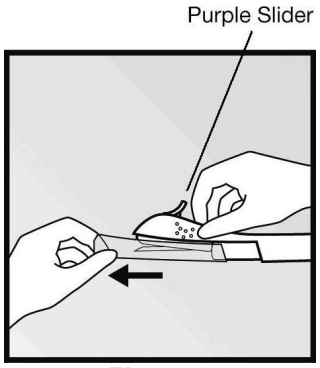


Figure 3

Step 8. With your free hand, stretch the skin around the insertion site with thumb and index finger (Figure 4).

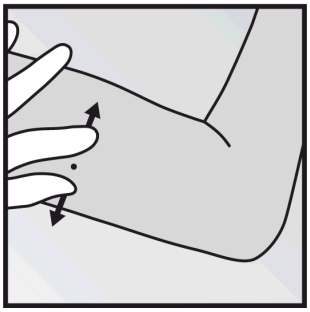


Figure 4

Step 9. Puncture the skin with the tip of the needle slightly angled less than 30° (Figure 5).

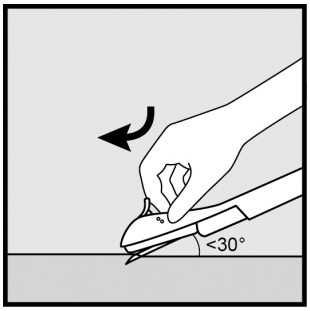


Figure 5

Step 10. Lower the applicator to a horizontal position. While lifting the skin with the tip of the needle (Figure 6), slide the needle to its full length. You may feel slight resistance but do not exert excessive force. **If the needle is not inserted to its full length, the implant will not be inserted properly.**

You can best see movement of the needle, and that it is inserted just under the skin, if you are seated and are looking at the applicator from the side and NOT from above. In this position, you can clearly see the insertion site and the movement of the needle just under the skin.

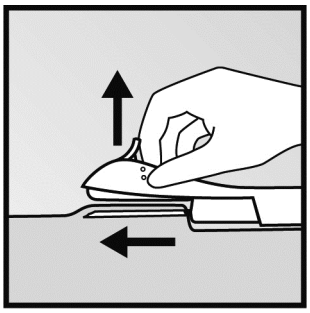


Figure 6

Step 11. Keep the applicator in the same position with the needle inserted to its full length. If needed, you may use your free hand to keep the applicator in the same position during the following procedure. Unlock the purple slider by pushing it slightly down. Move the slider fully back until it stops (Figure 7). The implant is now in its final subdermal position, and the needle is locked inside the body of the applicator. The applicator can now be removed. **If the applicator is not kept in the same position during this procedure or if the purple slider is not completely moved to the back, the implant will not be inserted properly.**

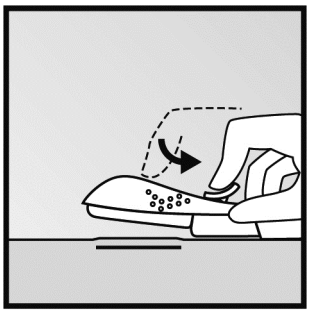


Figure 7

Step 12. **Always verify the presence of the implant in the woman's arm immediately after insertion by palpation.** By palpating both ends of the implant, you should be able to confirm the presence of the 4 cm rod (Figure 8). See "If the rod is not palpable" below.

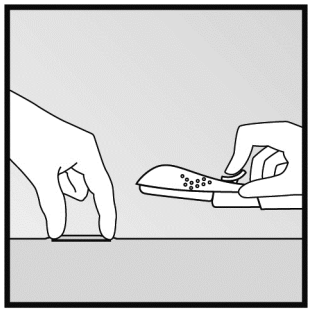


Figure 8

Step 13. Place a small adhesive bandage over the insertion site. Request that the woman palpate the implant.

Step 14. Apply a pressure bandage with sterile gauze to minimize bruising. The woman may remove the pressure bandage in 24 hours and the small bandage over the insertion site after 3 to 5 days.

Step 15. Complete the USER CARD and give it to the woman to keep. Also, complete the PATIENT CHART LABEL and affix it to the woman's medical record.

Step 16. The applicator is for single use only and should be disposed in accordance with the Center for Disease Control and Prevention guidelines for handling of hazardous waste.

If the rod is not palpable:

If you cannot feel the implant or are in doubt of its presence, the implant may not have been inserted or it may have been inserted deeply:

- Check the applicator. The needle should be fully retracted and only the purple tip of the obturator should be visible.
- Use other methods to confirm the presence of the implant. Given the radiopaque nature of the implant, suitable methods for localization are two-dimensional X-ray and X-ray computerized tomography (CT scan). Ultrasound scanning (USS) with a high-frequency linear array transducer (10 MHz or greater) or magnetic resonance imaging (MRI) may be used. If these methods fail, call 1-877-467-5266 for information on the procedure for measuring etonogestrel blood levels.

Until the presence of the implant has been verified, the woman should be advised to use a non-hormonal contraceptive method, such as condoms.

Once the non-palpable implant has been located, removal is recommended *[see Warnings and Precautions (5.1)]*.

2.3 Removal of NEXPLANON

Preparation

Before initiating the removal procedure, the healthcare provider should carefully read the instructions for removal and consult the USER CARD and/or the PATIENT CHART LABEL for the location of the implant. The exact location of the implant in the arm should be verified by palpation. *[See Dosage and Administration (2.3), Localization and Removal of a Non-Palpable Implant.]*

Procedure for Removal of an Implant that is Palpable

Before removal of the implant, the healthcare provider should confirm that:

- The woman does not have allergies to the antiseptic or anesthetic to be used.

Remove the implant under aseptic conditions.

The following equipment is needed for removal of the implant:

- An examination table for the woman to lie on
- Sterile surgical drapes, sterile gloves, antiseptic solution, sterile marker (optional)
- Local anesthetic, needles, and syringe
- Sterile scalpel, forceps (straight and curved mosquito)
- Skin closure, sterile gauze, adhesive bandage and pressure bandages

Removal Procedure

Step 1. Clean the site where the incision will be made and apply an antiseptic. Locate the implant by palpation and mark the distal end (end closest to the elbow), for example, with a sterile marker (Figure 9).

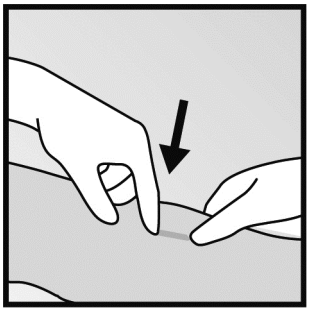


Figure 9

Step 2. Anesthetize the arm, for example, with 0.5 to 1 mL 1% lidocaine at the marked site where the incision will be made (Figure 10). Be sure to inject the local anesthetic under the implant to keep it close to the skin surface.

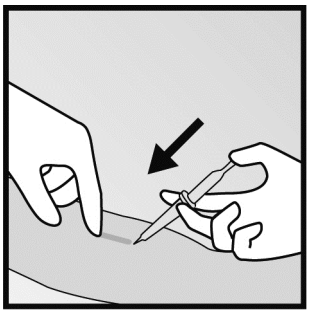


Figure 10

Step 3. Push down the proximal end of the implant (Figure 11) to stabilize it; a bulge may appear indicating the distal end of the implant. Starting at the distal tip of the implant, make a longitudinal incision of 2 mm towards the elbow.

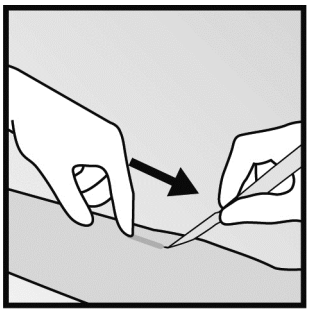


Figure 11

Step 4. Gently push the implant towards the incision until the tip is visible. Grasp the implant with forceps (preferably curved mosquito forceps) and gently remove the implant (Figure 12).

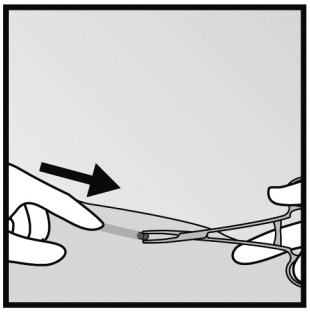


Figure 12

Step 5. If the implant is encapsulated, make an incision into the tissue sheath and then remove the implant with the forceps (Figures 13 and 14).

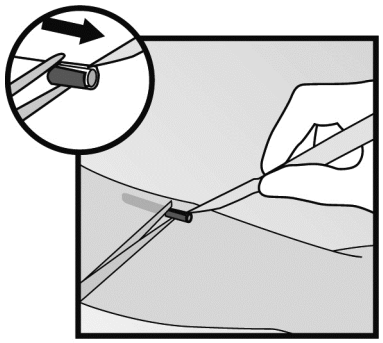


Figure 13

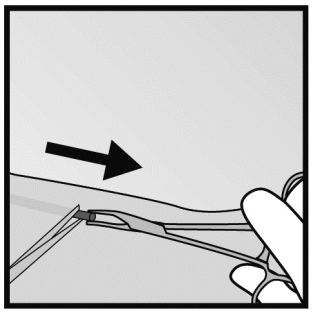


Figure 14

Step 6. If the tip of the implant does not become visible in the incision, gently insert a forceps into the incision (Figure 15). Flip the forceps over into your other hand (Figure 16).

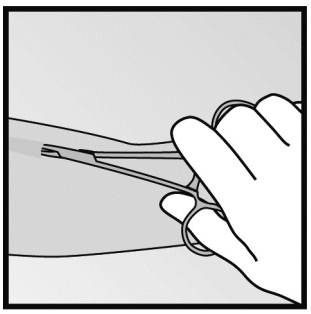


Figure 15

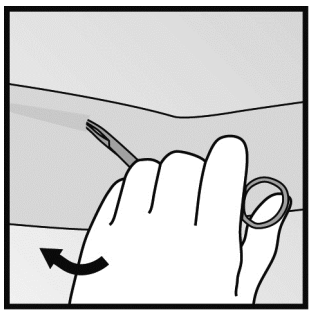


Figure 16

Step 7. With a second pair of forceps carefully dissect the tissue around the implant and grasp the implant (Figure 17). The implant can then be removed.

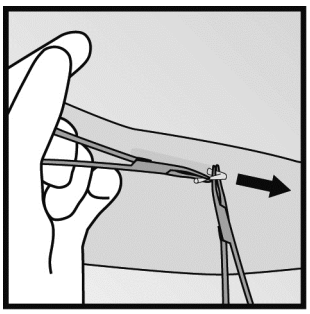


Figure 17

Step 8. Confirm that the entire implant, which is 4 cm long, has been removed by measuring its length. There have been reports of broken implants while in the patient's arm. In some cases, difficult removal of the broken implant has been reported. If a partial implant (less than 4 cm) is removed, the remaining piece should be removed by following the instructions in section 2.3. *[See Dosage and Administration (2.3).]* If the woman would like to continue using NEXPLANON, a new implant may be inserted immediately after the old implant is removed using the same incision *[see Dosage and Administration (2.4)]*.

Step 9. After removing the implant, close the incision with a steri-strip and apply an adhesive bandage.

Step 10. Apply a pressure bandage with sterile gauze to minimize bruising. The woman may remove the pressure bandage in 24 hours and the small bandage in 3 to 5 days.

Localization and Removal of a Non-Palpable Implant

There have been reports of migration of the implant; usually this involves minor movement relative to the original position *[see Warnings and Precautions (5.1)]*, but may lead to the implant not being palpable at the location in which it was placed. An implant that has been deeply inserted or has migrated may not be palpable and therefore imaging procedures, as described below, may be required for localization.

A non-palpable implant should always be located prior to attempting removal. Given the radiopaque nature of the implant, suitable methods for localization include two-dimensional X-ray and X-ray computer tomography (CT). Ultrasound scanning (USS) with a high-frequency linear array transducer (10 MHz or greater) or magnetic resonance imaging (MRI) may be used. Once the implant has been localized in the arm, the implant should be removed according to the instructions in *Dosage and Administration (2.3), Procedure for Removal of an Implant that is Palpable,* and the use of ultrasound guidance during the removal should be considered.

If the implant cannot be found in the arm after comprehensive localization attempts, consider applying imaging techniques to the chest as events of migration to the pulmonary vasculature have been reported. If the implant is located in the chest, surgical or endovascular procedures may be needed for removal; healthcare providers familiar with the anatomy of the chest should be consulted.

If at any time these imaging methods fail to locate the implant, etonogestrel blood level determination can be used for verification of the presence of the implant. For details on etonogestrel blood level determination, call 1-877-467-5266 for further instructions.

If the implant migrates within the arm, removal may require a minor surgical procedure with a larger incision or a surgical procedure in an operating room. Removal of deeply inserted implants should be conducted with caution in order to prevent injury to deeper neural or vascular structures in the arm and be performed by healthcare providers familiar with the anatomy of the arm.

Exploratory surgery without knowledge of the exact location of the implant is strongly discouraged.

2.4 Replacing NEXPLANON

Immediate replacement can be done after removal of the previous implant and is similar to the insertion procedure described in section 2.2 Insertion of NEXPLANON.

The new implant may be inserted in the same arm, and through the same incision from which the previous implant was removed. If the same incision is being used to insert a new implant, anesthetize the insertion site [for example, 2 mL lidocaine (1%)] applying it just under the skin along the 'insertion canal.'

Follow the subsequent steps in the insertion instructions *[see Dosage and Administration (2.2)]*.

3 DOSAGE FORMS AND STRENGTHS

Single, white/off-white, soft, radiopaque, flexible, ethylene vinyl acetate (EVA) copolymer implant, 4 cm in length and 2 mm in diameter containing 68 mg etonogestrel and 15 mg of barium sulfate.

Single, white/off-white, soft, radiopaque, flexible, ethylene vinyl acetate (EVA) copolymer implant, 4 cm in length and 2 mm in diameter containing 68 mg etonogestrel, 15 mg of barium sulfate and 0.1 mg of magnesium stearate.

4 CONTRAINDICATIONS

NEXPLANON should not be used in women who have

- Known or suspected pregnancy
- Current or past history of thrombosis or thromboembolic disorders
- Liver tumors, benign or malignant, or active liver disease
- Undiagnosed abnormal genital bleeding
- Known or suspected breast cancer, personal history of breast cancer, or other progestin-sensitive cancer, now or in the past
- Allergic reaction to any of the components of NEXPLANON *[see Adverse Reactions (6)]*

5 WARNINGS AND PRECAUTIONS

The following information is based on experience with the etonogestrel implants (IMPLANON and/or NEXPLANON), other progestin-only contraceptives, or experience with combination (estrogen plus progestin) oral contraceptives.

5.1 Complications of Insertion and Removal

NEXPLANON should be inserted subdermally so that it will be palpable after insertion, and this should be confirmed by palpation immediately after insertion. Failure to insert NEXPLANON properly may go unnoticed unless it is palpated immediately after insertion. Undetected failure to insert the implant may lead to an unintended pregnancy. Complications related to insertion and removal procedures, such as pain, paresthesias, bleeding, hematoma, scarring or infection, may occur.

If NEXPLANON is inserted deeply (intramuscular or in the fascia), neural or vascular injury may occur. To reduce the risk of neural or vascular injury, NEXPLANON should be inserted at the inner side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus. NEXPLANON should be inserted subdermally just under the skin avoiding the sulcus (groove) between the biceps and triceps muscles and the large blood vessels and nerves that lie there in the neurovascular bundle deeper in the subcutaneous tissues. Deep insertions of NEXPLANON have been associated with paraesthesia (due to neural injury), migration of the implant (due to intramuscular or fascial insertion), and intravascular insertion. If infection develops at the insertion site, start suitable treatment. If the infection persists, the implant should be removed. Incomplete insertions or infections may lead to expulsion.

Implant removal may be difficult or impossible if the implant is not inserted correctly, is inserted too deeply, not palpable, encased in fibrous tissue, or has migrated.

There have been reports of migration of the implant within the arm from the insertion site, which may be related to deep insertion. There also have been postmarketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular

insertion. In cases where the implant has migrated to the pulmonary artery, endovascular or surgical procedures may be needed for removal.

If at any time the implant cannot be palpated, it should be localized and removal is recommended.

Exploratory surgery without knowledge of the exact location of the implant is strongly discouraged. Removal of deeply inserted implants should be conducted with caution in order to prevent injury to deeper neural or vascular structures in the arm and be performed by healthcare providers familiar with the anatomy of the arm. If the implant is located in the chest, healthcare providers familiar with the anatomy of the chest should be consulted. Failure to remove the implant may result in continued effects of etonogestrel, such as compromised fertility, ectopic pregnancy, or persistence or occurrence of a drug-related adverse event.

5.2 Changes in Menstrual Bleeding Patterns

After starting NEXPLANON, women are likely to have a change from their normal menstrual bleeding pattern. These may include changes in bleeding frequency (absent, less, more frequent or continuous), intensity (reduced or increased) or duration. In clinical trials of the non-radiopaque etonogestrel implant (IMPLANON), bleeding patterns ranged from amenorrhea (1 in 5 women) to frequent and/or prolonged bleeding (1 in 5 women). The bleeding pattern experienced during the first three months of NEXPLANON use is broadly predictive of the future bleeding pattern for many women. Women should be counseled regarding the bleeding pattern changes they may experience so that they know what to expect. Abnormal bleeding should be evaluated as needed to exclude pathologic conditions or pregnancy.

In clinical studies of the non-radiopaque etonogestrel implant, reports of changes in bleeding pattern were the most common reason for stopping treatment (11.1%). Irregular bleeding (10.8%) was the single most common reason women stopped treatment, while amenorrhea (0.3%) was cited less frequently. In these studies, women had an average of 17.7 days of bleeding or spotting every 90 days (based on 3,315 intervals of 90 days recorded by 780 patients). The percentages of patients having 0, 1-7, 8-21, or >21 days of spotting or bleeding over a 90-day interval while using the non-radiopaque etonogestrel implant are shown in Table 1.

Table 1: Percentages of Patients With 0, 1-7, 8-21, or >21 Days of Spotting or Bleeding Over a 90-Day Interval While Using the Non-Radiopaque Etonogestrel Implant (IMPLANON)

Total Days of Spotting or Bleeding	Percentage of Patients		
	Treatment Days 91-180 (N = 745)	Treatment Days 271-360 (N = 657)	Treatment Days 631-720 (N = 547)
0 Days	19%	24%	17%
1-7 Days	15%	13%	12%
8-21 Days	30%	30%	37%
>21 Days	35%	33%	35%

Bleeding patterns observed with use of the non-radiopaque etonogestrel implant for up to 2 years, and the proportion of 90-day intervals with these bleeding patterns, are summarized in Table 2.

Table 2: Bleeding Patterns Using the Non-Radiopaque Etonogestrel Implant (IMPLANON) During the First 2 Years of Use*

BLEEDING PATTERNS	DEFINITIONS	%†
Infrequent	Less than three bleeding and/or spotting episodes in 90 days (excluding amenorrhea)	33.6
Amenorrhea	No bleeding and/or spotting in 90 days	22.2
Prolonged	Any bleeding and/or spotting episode lasting	17.7

	more than 14 days in 90 days	
Frequent	More than 5 bleeding and/or spotting episodes in 90 days	6.7

* Based on 3315 recording periods of 90 days duration in 780 women, excluding the first 90 days after implant insertion

† % = Percentage of 90-day intervals with this pattern

In case of undiagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy.

5.3 Ectopic Pregnancies

As with all progestin-only contraceptive products, be alert to the possibility of an ectopic pregnancy among women using NEXPLANON who become pregnant or complain of lower abdominal pain. Although ectopic pregnancies are uncommon among women using NEXPLANON, a pregnancy that occurs in a woman using NEXPLANON may be more likely to be ectopic than a pregnancy occurring in a woman using no contraception.

5.4 Thrombotic and Other Vascular Events

The use of combination hormonal contraceptives (progestin plus estrogen) increases the risk of vascular events, including arterial events (strokes and myocardial infarctions) or deep venous thrombotic events (venous thromboembolism, deep venous thrombosis, retinal vein thrombosis, and pulmonary embolism). NEXPLANON is a progestin-only contraceptive. It is unknown whether this increased risk is applicable to etonogestrel alone. It is recommended, however, that women with risk factors known to increase the risk of venous and arterial thromboembolism be carefully assessed.

There have been postmarketing reports of serious arterial thrombotic and venous thromboembolic events, including cases of pulmonary emboli (some fatal), deep vein thrombosis, myocardial infarction, and strokes, in women using etonogestrel implants. NEXPLANON should be removed in the event of a thrombosis.

Due to the risk of thromboembolism associated with pregnancy and immediately following delivery, NEXPLANON should not be used prior to 21 days postpartum. Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence.

Evaluate for retinal vein thrombosis immediately if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions.

Consider removal of the NEXPLANON implant in case of long-term immobilization due to surgery or illness.

5.5 Ovarian Cysts

If follicular development occurs, atresia of the follicle is sometimes delayed, and the follicle may continue to grow beyond the size it would attain in a normal cycle. Generally, these enlarged follicles disappear spontaneously. On rare occasion, surgery may be required.

5.6 Carcinoma of the Breast and Reproductive Organs

Women who currently have or have had breast cancer should not use hormonal contraception because breast cancer may be hormonally sensitive *[see Contraindications (4)]*. Some studies suggest that the use of combination hormonal contraceptives might increase the incidence of breast cancer; however, other studies have not confirmed such findings.

Some studies suggest that the use of combination hormonal contraceptives is associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings are due to differences in sexual behavior and other factors.

Women with a family history of breast cancer or who develop breast nodules should be carefully monitored.

5.7 Liver Disease

Disturbances of liver function may necessitate the discontinuation of hormonal contraceptive use until markers of liver function return to normal. Remove NEXPLANON if jaundice develops.

Hepatic adenomas are associated with combination hormonal contraceptives use. An estimate of the attributable risk is 3.3 cases per 100,000 for combination hormonal contraceptives users. It is not known whether a similar risk exists with progestin-only methods like NEXPLANON.

The progestin in NEXPLANON may be poorly metabolized in women with liver impairment. Use of NEXPLANON in women with active liver disease or liver cancer is contraindicated *[see Contraindications (4)]*.

5.8 Weight Gain

In clinical studies, mean weight gain in U.S. non-radiopaque etonogestrel implant (IMPLANON) users was 2.8 pounds after one year and 3.7 pounds after two years. How much of the weight gain was related to the non-radiopaque etonogestrel implant is unknown. In studies, 2.3% of the users reported weight gain as the reason for having the non-radiopaque etonogestrel implant removed.

5.9 Elevated Blood Pressure

Women with a history of hypertension-related diseases or renal disease should be discouraged from using hormonal contraception. For women with well-controlled hypertension, use of NEXPLANON can be considered. Women with hypertension using NEXPLANON should be closely monitored. If sustained hypertension develops during the use of NEXPLANON, or if a significant increase in blood pressure does not respond adequately to antihypertensive therapy, NEXPLANON should be removed.

5.10 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among combination hormonal contraceptive users. It is not known whether a similar risk exists with progestin-only methods like NEXPLANON.

5.11 Carbohydrate and Lipid Metabolic Effects

Use of NEXPLANON may induce mild insulin resistance and small changes in glucose concentrations of unknown clinical significance. Carefully monitor prediabetic and diabetic women using NEXPLANON.

Women who are being treated for hyperlipidemia should be followed closely if they elect to use NEXPLANON. Some progestins may elevate LDL levels and may render the control of hyperlipidemia more difficult.

5.12 Depressed Mood

Women with a history of depressed mood should be carefully observed. Consideration should be given to removing NEXPLANON in patients who become significantly depressed.

5.13 Return to Ovulation

In clinical trials with the non-radiopaque etonogestrel implant (IMPLANON), the etonogestrel levels in blood decreased below sensitivity of the assay by one week after removal of the implant. In addition, pregnancies were observed to occur as early as 7 to 14 days after removal. Therefore, a woman should re-start contraception immediately after removal of the implant if continued contraceptive protection is desired.

5.14 Fluid Retention

Hormonal contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention. It is unknown if NEXPLANON causes fluid retention.

5.15 Contact Lenses

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

5.16 *In Situ* Broken or Bent Implant

There have been reports of broken or bent implants while in the patient's arm. Based on *in vitro* data, when an implant is broken or bent, the release rate of etonogestrel may be slightly increased.

When an implant is removed, it is important to remove it in its entirety *[see Dosage and Administration (2.3)]*.

5.17 Monitoring

A woman who is using NEXPLANON should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated health care.

5.18 Drug-Laboratory Test Interactions

Sex hormone-binding globulin concentrations may be decreased for the first six months after NEXPLANON insertion followed by gradual recovery. Thyroxine concentrations may initially be slightly decreased followed by gradual recovery to baseline.

6 ADVERSE REACTIONS

The following adverse reactions reported with the use of hormonal contraception are discussed elsewhere in the labeling:

- Changes in Menstrual Bleeding Patterns *[see Warnings and Precautions (5.2)]*
- Ectopic Pregnancies *[see Warnings and Precautions (5.3)]*
- Thrombotic and Other Vascular Events *[see Warnings and Precautions (5.4)]*
- Liver Disease *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials involving 942 women who were evaluated for safety, change in menstrual bleeding patterns (irregular menses) was the most common adverse reaction causing discontinuation of use of the non-radiopaque etonogestrel implant (IMPLANON) (11.1% of women).

Adverse reactions that resulted in a rate of discontinuation of ≥1% are shown in Table 3.

Table 3: Adverse Reactions Leading to Discontinuation of Treatment in 1% or More of Subjects in Clinical Trials of the Non-Radiopaque Etonogestrel Implant (IMPLANON)

Adverse Reactions	All Studies N = 942
Bleeding Irregularities*	11.1%
Emotional Lability†	2.3%
Weight Increase	2.3%
Headache	1.6%
Acne	1.3%
Depression‡	1.0%

* Includes "frequent", "heavy", "prolonged", "spotting", and other patterns of bleeding irregularity.
†Among US subjects (N=330), 6.1% experienced emotional lability that led to discontinuation.
‡Among US subjects (N=330), 2.4% experienced depression that led to discontinuation.

Other adverse reactions that were reported by at least 5% of subjects in the non-radiopaque etonogestrel implant clinical trials are listed in Table 4.

Table 4: Common Adverse Reactions Reported by ≥5% of Subjects in Clinical Trials With the Non-Radiopaque Etonogestrel Implant (IMPLANON)

Adverse Reactions	All Studies N = 942
Headache	24.9%
Vaginitis	14.5%
Weight increase	13.7%
Acne	13.5%
Breast pain	12.8%
Abdominal pain	10.9%
Pharyngitis	10.5%
Leukorrhea	9.6%
Influenza-like symptoms	7.6%
Dizziness	7.2%
Dysmenorrhea	7.2%
Back pain	6.8%
Emotional lability	6.5%
Nausea	6.4%
Pain	5.6%
Nervousness	5.6%
Depression	5.5%
Hypersensitivity	5.4%
Insertion site pain	5.2%

In a clinical trial of NEXPLANON, in which investigators were asked to examine the implant site after insertion, implant site reactions were reported in 8.6% of women. Erythema was the most frequent implant site complication, reported during and/or shortly after insertion, occurring in 3.3% of subjects. Additionally, hematoma (3.0%), bruising (2.0%), pain (1.0%), and swelling (0.7%) were reported.

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of IMPLANON and NEXPLANON. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders: constipation, diarrhea, flatulence, vomiting.
General disorders and administration site conditions: edema, fatigue, implant site reaction, pyrexia.
Immune system disorders: anaphylactic reactions.
Infections and infestations: rhinitis, urinary tract infection.
Investigations: clinically relevant rise in blood pressure, weight decreased.
Metabolism and nutrition disorders: increased appetite.
Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal pain, myalgia.
Nervous system disorders: convulsions, migraine, somnolence.
Pregnancy, puerperium and perinatal conditions: ectopic pregnancy.
Psychiatric disorders: anxiety, insomnia, libido decreased.
Renal and urinary disorders: dysuria.
Reproductive system and breast disorders: breast discharge, breast enlargement, ovarian cyst, pruritus genital, vulvovaginal discomfort.
Skin and subcutaneous tissue disorders: angioedema, aggravation of angioedema and/or aggravation of hereditary angioedema, alopecia, chloasma, hypertrichosis, pruritus, rash, seborrhea, urticaria.
Vascular disorders: hot flush.

Complications related to insertion or removal of the etonogestrel implants reported include: bruising, slight local irritation, pain or itching, fibrosis at the implant site, paresthesia or paresthesia-like events, scarring and abscess. Expulsion or migration of the implant have been reported, including to the chest wall. In some cases, implants have been found within the vasculature, including the pulmonary artery. Some cases of implants found within the pulmonary artery reported chest pain and/or dyspnea; others have been reported as asymptomatic *[see Warnings and Precautions (5.1)]*. Surgical intervention might be necessary when removing the implant.

7 DRUG INTERACTIONS

7.1 Changes in Contraceptive Effectiveness Associated With Coadministration of Other Products

Drugs or herbal products that induce enzymes, including CYP3A4, that metabolize progestins may decrease the plasma concentrations of progestins, and may decrease the effectiveness of NEXPLANON. In women on long-term treatment with hepatic enzyme inducing drugs, it is recommended to remove the implant and to advise a contraceptive method that is unaffected by the interacting drug.

Some of these drugs or herbal products that induce enzymes, including CYP3A4, include:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's wort
- topiramate

HIV Antiretrovirals

Significant changes (increase or decrease) in the plasma levels of progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors. Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.2 Increase in Plasma Concentrations of Etonogestrel Associated With Coadministered Drugs

CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma concentrations of etonogestrel.

7.3 Changes in Plasma Concentrations of Coadministered Drugs

Hormonal contraceptives may affect the metabolism of other drugs. Consequently, plasma concentrations may either increase (for example, cyclosporin) or decrease (for example, lamotrigine). Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

NEXPLANON is not indicated for use during pregnancy *[see Contraindications (4)]*.

Teratology studies have been performed in rats and rabbits using oral administration up to 390 and 790 times the human etonogestrel dose (based upon body surface), respectively, and revealed no evidence of fetal harm due to etonogestrel exposure.

Studies have revealed no increased risk of birth defects in women who have used combination oral contraceptives before pregnancy or during early pregnancy. There is no evidence that the risk associated with etonogestrel is different from that of combination oral contraceptives.

NEXPLANON should be removed if maintaining a pregnancy.

8.3 Nursing Mothers

Based on limited clinical data, NEXPLANON may be used during breastfeeding after the fourth postpartum week. Use of NEXPLANON before the fourth postpartum week has not been studied. Small amounts of etonogestrel are excreted in breast milk. During the first months after insertion of NEXPLANON, when maternal blood levels of etonogestrel are highest, about 100 ng of etonogestrel may be ingested by the child per day based on an average daily milk ingestion of 658 mL. Based on daily milk ingestion of 150 mL/kg, the mean daily infant etonogestrel dose one month after insertion of the non-radiopaque etonogestrel implant (IMPLANON) is about 2.2% of the weight-adjusted maternal daily dose, or about 0.2% of the estimated absolute maternal daily dose. The health of breastfed infants whose mothers began using the non-radiopaque etonogestrel implant during the fourth to eighth week postpartum (n=38) was evaluated in a comparative study with infants of mothers using a non-hormonal IUD (n=33). They were breastfed for a mean duration of 14 months and followed up to 36 months of age. No significant effects and no differences between the groups were observed on the physical and psychomotor development of these infants. No differences between groups in the production or quality of breast milk were detected.

Healthcare providers should discuss both hormonal and non-hormonal contraceptive options, as steroids may not be the initial choice for these patients.

8.4 Pediatric Use

Safety and efficacy of NEXPLANON have been established in women of reproductive age. Safety and efficacy of NEXPLANON are expected to be the same for postpubertal adolescents. However, no clinical studies have been conducted in women less than 18 years of age. Use of this product before menarche is not indicated.

8.5 Geriatric Use

This product has not been studied in women over 65 years of age and is not indicated in this population.

8.6 Hepatic Impairment

No studies were conducted to evaluate the effect of hepatic disease on the disposition of NEXPLANON. The use of NEXPLANON in women with active liver disease is contraindicated *[see Contraindications (4)]*.

8.7 Renal Impairment

No studies were conducted to evaluate the effect of renal disease on the disposition of NEXPLANON.

8.8 Overweight Women

The effectiveness of the etonogestrel implant in women who weighed more than 130% of their ideal body weight has not been defined because such women were not studied in clinical trials. Serum concentrations of etonogestrel are inversely related to body weight and decrease with time after implant insertion. It is therefore possible that NEXPLANON may be less effective in overweight women, especially in the presence of other factors that decrease serum etonogestrel concentrations such as concomitant use of hepatic enzyme inducers.

10 OVERDOSAGE

Overdosage may result if more than one implant is inserted. In case of suspected overdose, the implant should be removed.

11 DESCRIPTION

NEXPLANON is a radiopaque, progestin-only, soft, flexible implant preloaded in a sterile, disposable applicator for subdermal use. The implant is white/off-white, non-biodegradable and 4 cm in length with a diameter of 2 mm (see Figure 18). Each implant consists of an ethylene vinyl acetate (EVA) copolymer core, containing 68 mg of the synthetic progestin etonogestrel, barium sulfate (radiopaque ingredient), and may also contain magnesium stearate, surrounded by an EVA copolymer skin. Once inserted subdermally, the release rate is 60-70 mcg/day in week 5-6 and decreases to approximately 35-45 mcg/day at the end of the first year, to approximately 30-40 mcg/day at the end of the second year, and then to approximately 25-30 mcg/day at the end of the third year. NEXPLANON is a progestin-only contraceptive and does not contain estrogen. NEXPLANON does not contain latex.

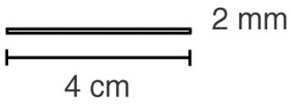


Figure 18 (Not to scale)

Etonogestrel [13-Ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one], structurally derived from 19-nortestosterone, is the synthetic biologically active metabolite of the synthetic progestin desogestrel. It has a molecular weight of 324.46 and the following structural formula (Figure 19).

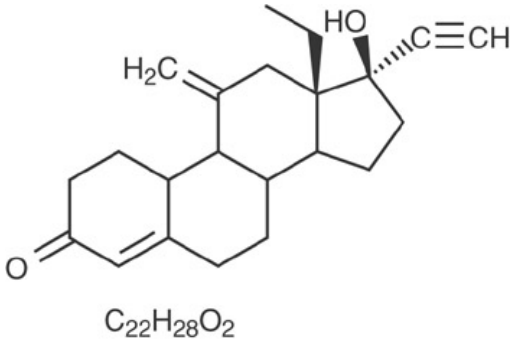


Figure 19

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The contraceptive effect of NEXPLANON is achieved by suppression of ovulation, increased viscosity of the cervical mucus, and alterations in the endometrium.

12.2 Pharmacodynamics

Exposure-response relationships of NEXPLANON are unknown.

12.3 Pharmacokinetics

Absorption

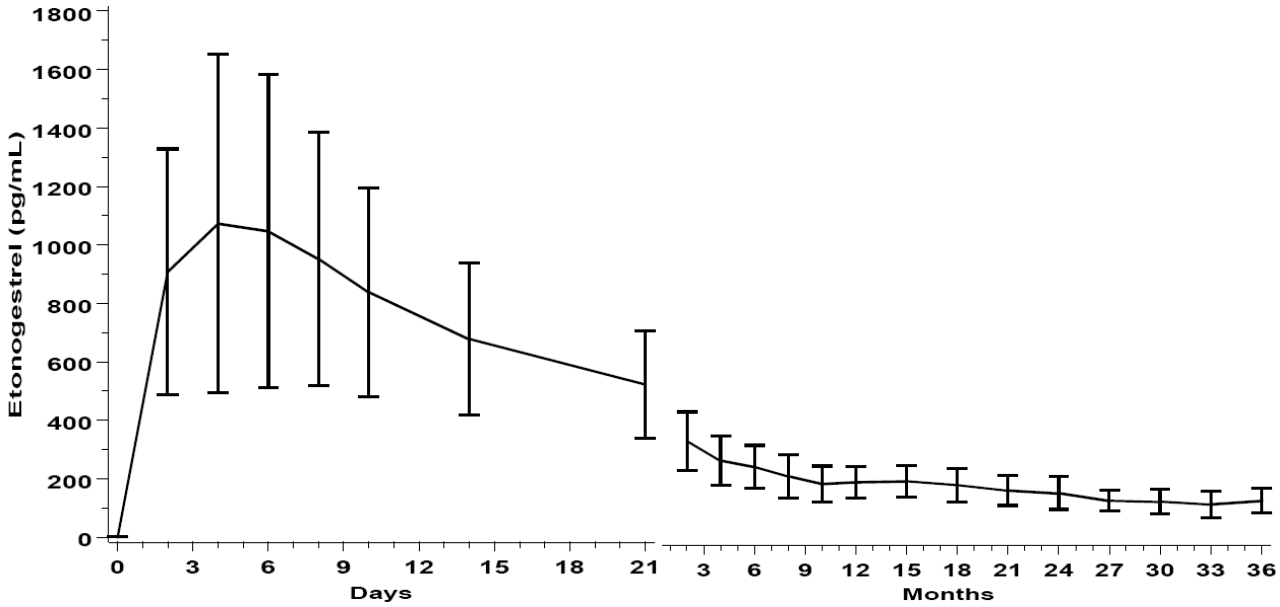
After subdermal insertion of the etonogestrel implant, etonogestrel is released into the circulation and is approximately 100% bioavailable.

In a three year clinical trial, NEXPLANON and the non-radiopaque etonogestrel implant (IMPLANON) yielded comparable systemic exposure to etonogestrel. For NEXPLANON, the mean (± SD) maximum serum etonogestrel concentrations were 1200 (± 604) pg/mL and were reached within the first two weeks after insertion (n=50). The mean (± SD) serum etonogestrel concentration decreased gradually over time, declining to 202 (± 55) pg/mL at 12 months (n=41), 164 (± 58) pg/mL at 24 months (n=37), and 138 (± 43) pg/mL at 36 months (n=32). For the non-radiopaque etonogestrel implant (IMPLANON), the mean (± SD)

maximum serum etonogestrel concentrations were 1145 (± 577) pg/mL and were reached within the first two weeks after insertion (n=53). The mean (± SD) serum etonogestrel concentration decreased gradually over time, declining to 223 (± 73) pg/mL at 12 months (n=40), 172 (± 77) pg/mL at 24 months (n=32), and 153 (± 52) pg/mL at 36 months (n=30).

The pharmacokinetic profile of NEXPLANON is shown in Figure 20.

Figure 20: Mean (± SD) Serum Concentration-Time Profile of Etonogestrel After Insertion of NEXPLANON During 3 Years of Use



Distribution

The apparent volume of distribution averages about 201 L. Etonogestrel is approximately 32% bound to sex hormone binding globulin (SHBG) and 66% bound to albumin in blood.

Metabolism

In vitro data shows that etonogestrel is metabolized in liver microsomes by the cytochrome P450 3A4 isoenzyme. The biological activity of etonogestrel metabolites is unknown.

Excretion

The elimination half-life of etonogestrel is approximately 25 hours. Excretion of etonogestrel and its metabolites, either as free steroid or as conjugates, is mainly in urine and to a lesser extent in feces. After removal of the implant, etonogestrel concentrations decreased below sensitivity of the assay by one week.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study in rats with subdermal implants releasing 10 and 20 mcg etonogestrel per day (equal to approximately 1.8-3.6 times the systemic steady state exposure in women using NEXPLANON), no drug-related carcinogenic potential was observed. Etonogestrel was not genotoxic in the *in vitro* Ames/Salmonella reverse mutation assay, the chromosomal aberration assay in Chinese hamster ovary cells or in the *in vivo* mouse micronucleus test. Fertility in rats returned after withdrawal from treatment.

14 CLINICAL STUDIES

14.1 Pregnancy

In clinical trials of up to 3 years duration that involved 923 subjects, 18-40 years of age at entry, and 1756 women-years of use with the non-radiopaque etonogestrel implant (IMPLANON), the total exposures expressed as 28-day cycle equivalents by study year were:

Year 1: 10,866 cycles
Year 2: 8,581 cycles
Year 3: 3,442 cycles

The clinical trials excluded women who:

- Weighed more than 130% of their ideal body weight
- Were chronically taking medications that induce liver enzymes

In the subgroup of women, 18-35 years of age at entry, 6 pregnancies during 20,648 cycles of use were reported. Two pregnancies occurred in each of Years 1, 2, and 3. Each conception was likely to have occurred shortly before or within 2 weeks after removal of the non-radiopaque etonogestrel implant. With these 6 pregnancies, the cumulative Pearl Index was 0.38 pregnancies per 100 women-years of use.

14.2 Return to Ovulation

In clinical trials with the non-radiopaque etonogestrel implant (IMPLANON), the etonogestrel levels in blood decreased below sensitivity of the assay by one week after removal of the implant. In addition, pregnancies were observed to occur as early as 7 to 14 days after removal. Therefore, a woman should re-start contraception immediately after removal of the implant if continued contraceptive protection is desired.

14.3 Implant Insertion and Removal Characteristics

Out of 301 insertions of the NEXPLANON implant in a clinical trial, the mean insertion time (from the removal of the protection cap of the applicator until retraction of the needle from the arm) was 27.9 ± 29.3 seconds. After insertion, 300 out of 301 (99.7%) NEXPLANON implants were palpable. The single, non-palpable implant was not inserted according to the instructions.

For 112 out of 114 (98.2%) subjects in 2 clinical trials for whom insertion and removal data were available, NEXPLANON implants were clearly visible with use of two-dimensional x-ray after insertion. The two implants that were not clearly visible after insertion were clearly visible with two-dimensional x-ray before removal.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NEXPLANON is supplied as follows:

NDC 0052-0274-01

One NEXPLANON package consists of a single implant containing 68 mg etonogestrel and 15 mg of barium sulfate that is 4 cm in length and 2 mm in diameter, which is pre-loaded in the needle of a disposable applicator. The sterile applicator containing the implant is packed in a blister pack.

NDC 0052-4330-01

One NEXPLANON package consists of a single implant containing 68 mg etonogestrel, 15 mg of barium sulfate and 0.1 mg of magnesium stearate that is 4 cm in length and 2 mm in diameter, which is pre-loaded in the needle of a disposable applicator. The sterile applicator containing the implant is packed in a blister pack.

16.2 Storage and Handling

Store NEXPLANON (etonogestrel implant) Radiopaque at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) [see USP Controlled Room Temperature]. Avoid storing NEXPLANON at temperatures above 30ºC (86ºF).

17 PATIENT COUNSELING INFORMATION

Information for Patients

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- Counsel women about the insertion and removal procedure of the NEXPLANON implant. Provide the woman with a copy of the Patient Labeling and ensure that she understands the information in the Patient Labeling before insertion and removal. A USER CARD and consent form are included in the packaging. Have the woman complete a consent form and retain it in your records. The USER CARD should be filled out and given to the woman after insertion of the NEXPLANON implant so that she will have a record of the location of the implant in the upper arm and when it should be removed.

- Counsel women to contact their healthcare provider immediately if, at any time, they are unable to palpate the implant.

- Counsel women that NEXPLANON does not protect against HIV infection (AIDS) or other sexually transmitted diseases.

- Counsel women that the use of NEXPLANON may be associated with changes in their normal menstrual bleeding patterns so that they know what to expect.

FDA-Approved Patient Labeling

See the full patient product information for NEXPLANON.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by: N.V. Organon, Oss, The Netherlands, a subsidiary of **Merck & Co., Inc.**, Whitehouse Station, NJ 08889, USA

For patent information: www.merck.com/product/patent/home.html

uspi-mk8415-iptx-1612r018

EXHIBIT G

FDA-Approved Patient Labeling

NEXPLANON® (etonogestrel implant)
Radiopaque
Subdermal Use Only

NEXPLANON® does not protect against HIV infection (the virus that causes AIDS) or other sexually transmitted diseases.
Read this Patient Information leaflet carefully before you decide if NEXPLANON is right for you. This information does not take the place of talking with your healthcare provider. If you have any questions about NEXPLANON, ask your healthcare provider.

What is NEXPLANON?
NEXPLANON is a hormone-releasing birth control implant for use by women to prevent pregnancy for up to 3 years. The implant is a flexible plastic rod about the size of a matchstick that contains a progestin hormone called etonogestrel. It contains a small amount of barium sulfate so that the implant can be seen by X-ray, and may also contain magnesium stearate. Your healthcare provider will insert the implant just under the skin of the inner side of your upper arm. You can use a single NEXPLANON implant for up to 3 years. NEXPLANON does not contain estrogen.

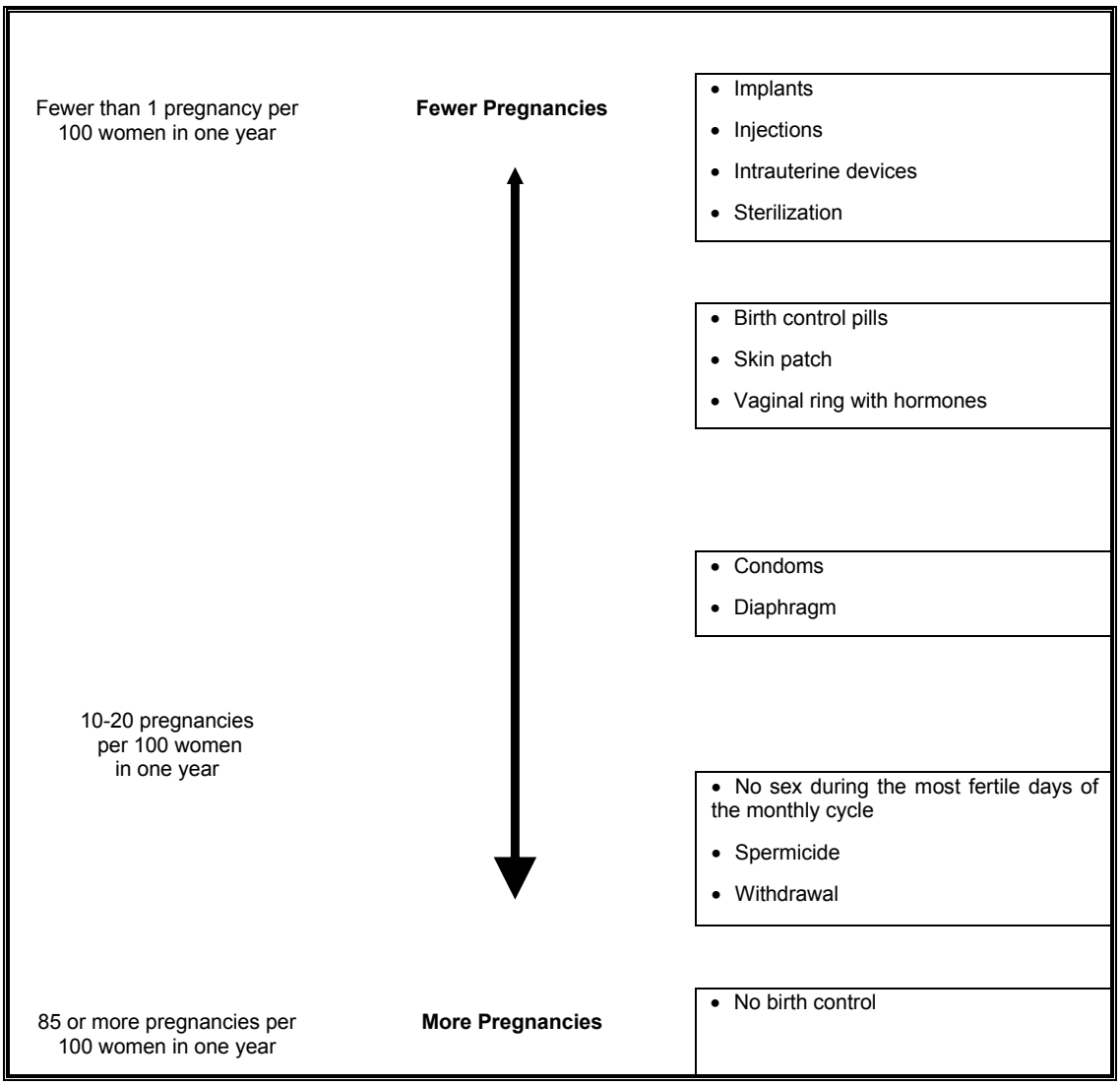
What if I need birth control for more than 3 years?
The NEXPLANON implant must be removed after 3 years. Your healthcare provider can insert a new implant under your skin after taking out the old one if you choose to continue using NEXPLANON for birth control.

What if I change my mind about birth control and want to stop using NEXPLANON before 3 years?
Your healthcare provider can remove the implant at any time. You may become pregnant as early as the first week after removal of the implant. If you do not want to get pregnant after your healthcare provider removes the NEXPLANON implant, you should start another birth control method right away.

How does NEXPLANON work?
NEXPLANON prevents pregnancy in several ways. The most important way is by stopping the release of an egg from your ovary. NEXPLANON also thickens the mucus in your cervix and this change may keep sperm from reaching the egg. NEXPLANON also changes the lining of your uterus.

How well does NEXPLANON work?
When the NEXPLANON implant is placed correctly, your chance of getting pregnant is very low (less than 1 pregnancy per 100 women who use NEXPLANON for 1 year). It is not known if NEXPLANON is as effective in very overweight women because studies did not include many overweight women.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



Who should not use NEXPLANON?

Do not use NEXPLANON if you:

- Are pregnant or think you may be pregnant
- Have, or have had blood clots, such as blood clots in your legs (deep venous thrombosis), lungs (pulmonary embolism), eyes (total or partial blindness), heart (heart attack), or brain (stroke)
- Have liver disease or a liver tumor
- Have unexplained vaginal bleeding
- Have breast cancer or any other cancer that is sensitive to progestin (a female hormone), now or in the past
- Are allergic to anything in NEXPLANON

Tell your healthcare provider if you have or have had any of the conditions listed above. Your healthcare provider can suggest a different method of birth control.

In addition, talk to your healthcare provider about using NEXPLANON if you:

- Have diabetes
- Have high cholesterol or triglycerides
- Have headaches
- Have gallbladder or kidney problems
- Have a history of depressed mood
- Have high blood pressure
- Have an allergy to numbing medicines (anesthetics) or medicines used to clean your skin (antiseptics). These medicines will be used when the implant is placed into or removed from your arm.

Interaction with Other Medicines
Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Certain medicines may make NEXPLANON less effective, including:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's wort
- topiramate
- HIV medicines

Ask your healthcare provider if you are not sure if your medicine is one listed above.

If there are medicines that you have been taking for a long time, that make NEXPLANON less effective, tell your healthcare provider. Your healthcare provider may remove the NEXPLANON implant and recommend a birth control method that can be used effectively with these medicines.

When you are using NEXPLANON, tell all of your healthcare providers that you have NEXPLANON in place in your arm.

How is the NEXPLANON implant placed and removed?
Your healthcare provider will place and remove the NEXPLANON implant in a minor surgical procedure in his or her office. The implant is placed just under the skin on the inner side of your upper arm.

The timing of insertion is important. Your healthcare provider may:
- Perform a pregnancy test before inserting NEXPLANON
- Schedule the insertion at a specific time of your menstrual cycle (for example, within the first days of your regular menstrual bleeding)

Your healthcare provider will cover the site where NEXPLANON was placed with 2 bandages. Leave the top bandage on for 24 hours. Keep the smaller bandage clean, dry, and in place for 3 to 5 days.

Immediately after the NEXPLANON implant has been placed, you and your healthcare provider should check that the implant is in your arm by feeling for it.

If you cannot feel the implant immediately after insertion, the implant may not have been inserted, or it may have been inserted deeply. A deep insertion may cause problems with locating and removing the implant. Once the healthcare professional has located the implant, removal may be recommended.

If at any time you cannot feel the NEXPLANON implant, contact your healthcare provider immediately and use a non-hormonal birth control method (such as condoms) until your healthcare provider confirms that the implant is in place. You may need special tests to check that the implant is in place or to help find the implant when it is time to take it out. If the implant cannot be found in the arm after a thorough search, your healthcare professional may use x-rays or other imaging methods on your chest.

Depending on the exact position of the implant, removal may be difficult and may require surgery.

You will be asked to review and sign a consent form prior to inserting the NEXPLANON implant. You will also get a USER CARD to keep at home with your health records. Your healthcare provider will fill out the USER CARD with the date the implant was inserted and the date the implant is to be removed. Keep track of the date the implant is to be removed. Schedule an appointment with your healthcare provider to remove the implant on or before the removal date.

Be sure to have checkups as advised by your healthcare provider.

What are the most common side effects I can expect while using NEXPLANON?

- **Changes in Menstrual Bleeding Patterns (menstrual periods)**

The most common side effect of NEXPLANON is a change in your normal menstrual bleeding pattern. In studies, one out of ten women stopped using the implant because of an unfavorable change in their bleeding pattern. You may experience longer or

shorter bleeding during your periods or have no bleeding at all. The time between periods may vary, and in between periods you may also have spotting.

Tell your healthcare provider right away if:
- You think you may be pregnant
- Your menstrual bleeding is heavy and prolonged

Besides changes in menstrual bleeding patterns, other frequent side effects that caused women to stop using the implant include:
- Mood swings
- Weight gain
- Headache
- Acne
- Depressed mood

Other common side effects include:
- Headache
- Vaginitis (inflammation of the vagina)
- Weight gain
- Acne
- Breast pain
- Viral infections such as sore throats or flu-like symptoms
- Stomach pain
- Painful periods
- Mood swings, nervousness, or depressed mood
- Back pain
- Nausea
- Dizziness
- Pain
- Pain at the site of insertion

Implants have been reported to be found in a blood vessel, including a blood vessel in the lung.
This is not a complete list of possible side effects. For more information, ask your healthcare provider for advice about any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088.

What are the possible risks of using NEXPLANON?

- **Problems with Insertion and Removal**

The implant may not be placed in your arm at all due to a failed insertion. If this happens, you may become pregnant. Immediately after insertion, and with help from your healthcare provider, you should be able to feel the implant under your skin. If you can't feel the implant, tell your healthcare provider.

Location and removal of the implant may be difficult or impossible because the implant is not where it should be. Special procedures, including surgery in the hospital, may be needed to remove the implant. If the implant is not removed, then the effects of NEXPLANON will continue for a longer period of time.

Implants have been found in the pulmonary artery (a blood vessel in the lung). If the implant cannot be found in the arm, your healthcare professional may use x-rays or other imaging methods on the chest. If the implant is located in the chest, surgery may be needed.

Other problems related to insertion and removal are:
- Pain, irritation, swelling, or bruising at the insertion site
- Scarring, including a thick scar called a keloid around the insertion site
- Infection
- Scar tissue may form around the implant making it difficult to remove
- The implant may come out by itself. You may become pregnant if the implant comes out by itself. Use a back up birth control method and call your healthcare provider right away if the implant comes out.
- The need for surgery in the hospital to remove the implant
- Injury to nerves or blood vessels in your arm
- The implant breaks making removal difficult

- **Ectopic Pregnancy**

If you become pregnant while using NEXPLANON, you have a slightly higher chance that the pregnancy will be ectopic (occurring outside the womb) than do women who do not use birth control. Unusual vaginal bleeding or lower stomach (abdominal) pain may be a sign of ectopic pregnancy. Ectopic pregnancy is a medical emergency that often requires surgery. Ectopic pregnancies can cause serious internal bleeding, infertility, and even death. Call your healthcare provider right away if you think you are pregnant or have unexplained lower stomach (abdominal) pain.

- **Ovarian Cysts**

Cysts may develop on the ovaries and usually go away without treatment but sometimes surgery is needed to remove them.

- **Breast Cancer**

It is not known whether NEXPLANON use changes a woman's risk for breast cancer. If you have breast cancer now, or have had it in the past, do not use NEXPLANON because some breast cancers are sensitive to hormones.

- **Serious Blood Clots**

NEXPLANON may increase your chance of serious blood clots, especially if you have other risk factors such as smoking. It is possible to die from a problem caused by a blood clot, such as a heart attack or a stroke.

Some examples of serious blood clots are blood clots in the:

- Legs (deep vein thrombosis)
- Lungs (pulmonary embolism)
- Brain (stroke)
- Heart (heart attack)
- Eyes (total or partial blindness)

The risk of serious blood clots is increased in women who smoke. If you smoke and want to use NEXPLANON, you should quit. Your healthcare provider may be able to help.

Tell your healthcare provider at least 4 weeks before if you are going to have surgery or will need to be on bed rest. You have an increased chance of getting blood clots during surgery or bed rest.

- **Other Risks**

A few women who use birth control that contains hormones may get:

- High blood pressure
- Gallbladder problems
- Rare cancerous or noncancerous liver tumors

- **Broken or Bent Implant**

If you feel that the implant may have broken or bent while in your arm, contact your healthcare provider.

When should I call my healthcare provider?

Call your healthcare provider right away if you have:

- Pain in your lower leg that does not go away
- Severe chest pain or heaviness in the chest
- Sudden shortness of breath, sharp chest pain, or coughing blood
- Symptoms of a severe allergic reaction, such as swollen face, tongue or throat; trouble breathing or swallowing
- Sudden severe headache unlike your usual headaches
- Weakness or numbness in your arm, leg, or trouble speaking
- Sudden partial or complete blindness
- Yellowing of your skin or whites of your eyes, especially with fever, tiredness, loss of appetite, dark colored urine, or light colored bowel movements
- Severe pain, swelling, or tenderness in the lower stomach (abdomen)
- Lump in your breast
- Problems sleeping, lack of energy, tiredness, or you feel very sad
- Heavy menstrual bleeding

What if I become pregnant while using NEXPLANON?

You should see your healthcare provider right away if you think that you may be pregnant. It is important to remove the implant and make sure that the pregnancy is not ectopic (occurring outside the womb). Based on experience with other hormonal contraceptives, NEXPLANON is not likely to cause birth defects.

Can I use NEXPLANON when I am breastfeeding?

If you are breastfeeding your child, you may use NEXPLANON if 4 weeks have passed since you had your baby. A small amount of the hormone contained in NEXPLANON passes into your breast milk. The health of breast-fed children whose mothers were using the implant has been studied up to 3 years of age in a small number of children. No effects on the growth and development of the children were seen. If you are breastfeeding and want to use NEXPLANON, talk with your healthcare provider for more information.

Additional Information

This Patient Information leaflet contains important information about NEXPLANON. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider for information about NEXPLANON that is written for healthcare professionals. You may also call 1-877-467-5266 or visit www.NEXPLANON-USA.com.

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Manufactured by: N.V. Organon, Oss, The Netherlands, a subsidiary of **Merck & Co., Inc.**, Whitehouse Station, NJ 08889, USA

For patent information: www.merck.com/product/patent/home.html

Revised: 03/2016

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